

A Psychosocial Approach to Understanding Causality Assessment in Early
Phase Oncology Clinical Trials: A Phenomenological Study

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ABSTRACT

Research Question: What are the psychosocial factors that affect causality assessment in early phase oncology clinical trials?

Methods: Thirty-two qualitative interviews were explicated with the aid of “Naturalistic Decision Making”. Data explication consisted of phenomenological reduction, delineating and clustering meaning units, forming themes, and creating a composite summary. Participants were members of the National Cancer Institute of Canada’s Clinical Trial Group Investigative New Drug committee.

Results: The process of assigning causality is extremely subjective and full of uncertainty. Physicians had no formal training, nor a tool to assist them with this process. Physicians were apprehensive about their decisions and felt pressure from their patients, as well as the pharmaceutical companies sponsoring the trial.

Conclusions: There are many problem areas when attributing causality, all of which have serious consequences, but clinicians used a variety of methods to cope with these problem areas.

Key Words: Psychosocial, oncology, causality, decision-making, phenomenology

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Introduction

The Process of Clinical Trials

A clinical trial is defined as a prospective research study that aims to answer a specific health question by examining the effect and value of an intervention(s) on human subjects.¹⁻³ Clinical trials are considered to be on the top of the health research hierarchy. Clinical trials lead the way in comparison to other health research methods because they address risk benefit ratios, a key aspect in intervention and patient safety.^{1,4} Clinical trials are deemed imperative for the study of new medications because they have strong implications for efficacy, safety, and clinical practice.¹

Clinical trials are performed in a wide range of health research avenues and typically involve a large group of professionals. These professionals include laboratory scientists, who work to understand the epidemiology of disease, as well as develop treatments; front-line doctors, nurses and other health care professionals, who work to conduct the clinical trials tests; pathologists, medical laboratory staff and informaticians, who study adverse events; as well as epidemiologists, statisticians, and biologists, who assess the cost benefit ratio of the treatment.⁵ Beyond this, there are also organizations and personnel responsible for funding, marketing and post-market analysis.⁶ Clinical trials involve a lengthy and detailed drug development process, which consist of four primary phases, all of which are separate trials in the overall process (see Table 1.1 below for a brief summary). The first phase of drug development commences the testing of the actual intervention. This intervention could be tested for the first

time, or could have had previous clinical trial exposure, but is being tested in a different medical setting (e.g., a different pathology).⁵ In this phase, a maximally tolerated dose (MTD) needs to be established.¹ MTD determines the maximum dose of a drug that can be administered before an unacceptable toxicity level is reached.¹ This trial is typically small, involving anywhere from 10-80 patients, with no control group.⁶ Once the safety of a drug and the MTD is determined, the drug development process can progress to phase II. In phase II, measurements of biologic activity and causality of adverse events are assessed in order to further establish the safety of the intervention, involving 50-300 patients, again with no control group.¹ Phase I and phase II of the drug development process will be the main focus of this research study. The level of safety involved in drug testing increases in each phase of oncology clinical trials; therefore, more patients can be involved in each phase, due to the lower risk of harm.⁶ In phases I and II, a control is not required. It is typically in phase III that a randomized trial is first introduced. In phase III, the intervention is then tested on hundreds to thousands of patients.⁵ The focus of this trial is to evaluate the effectiveness of the intervention in comparison to standardized treatment methods and continue to monitor adverse events.

Table 1 Stages of Drug Development

Phase	Objectives	Size	Control/No Control
Phase 1	Maximally Tolerated Dose (MTD) is determined	10-80 participants	No control
Phase 2	Measure biologic activity and adverse events	50-300 participants	No control
Phase 3	Evaluate effectiveness of the intervention	100s-1000s of participants	Control
Phase 4	Long term surveillance of the intervention	Unknown	Control

The final stage of drug development involves long-term surveillance of the intervention.¹ In this stage, the intervention is legalized and entered into the market.^{5,6} This is also known as the post-marketing analysis phase. This phase often goes unrecognized as a primary phase in the drug development process. It is typically given very little attention, unless an issue with adverse events arises, as resources are often limited.^{1,5,6}

While the focus of this review is on phase I and II clinical trials, it is important to review the entire drug development process and appreciate that each phase is subsequently reliant on the previous phase, and the quality of the trial, as well as the patients well-being, depend on the optimal execution of each and every stage. Oncology clinical trials aim to develop interventions that can be used for detecting, monitoring, preventing, and treating cancer.⁷ Clinical trials are also used in the field of oncology to enhance clinical practice, expand the market, and augment current ways of thinking about cancer epidemiology.⁷ In order for clinical trials to be successful and to have a significant impact on these various aspects of oncology, all phases of the drug development process need to be carried out to the best of their potential and as efficiently as possible. Clinical trials that are poorly executed result in little to no advancement in clinical practice, are a waste of financial resources and are criticized on aspects of validity and ethics.⁷

The History of Clinical Trials and their Prevalence in Canada Today

Clinical trials have a long history, which dates back to the first reported clinical trial in 1747.⁸ James Lind, a Scottish physician, performed the first clinical trial while at sea onboard the H.M.S. Salisbury. He was only on the ship for a few months when multiple sailors became sick with what was later documented as scurvy.⁸ Lind was in search of a cure and, in doing so, conducted an experiment where he controlled the dietary intake of several personnel onboard in order to determine which diet would alleviate symptoms.⁸ Clinical trials have since progressed to include placebos, first reported in 1863, as well as randomization, which was introduced by Fisher in 1923 while studying pulmonary tuberculosis.⁸ It was during World War II that clinical trials became a standard practice for evaluating medical interventions.⁸ Significant methodological advancements have been made since the first clinical trial, emphasizing patient safety, ethics, as well as standard protocols and procedures. However, there is still a strong need to continue to improve the clinical trial process.

Oncology clinical trials play a large role in the Canadian health care system. According to the Canadian Cancer Society, as of July 2010 a total of 1177 oncology clinical trials are currently taking place in Canada (see Table 1.2 for a breakdown by province).⁹ If all of these trials progress to phase II, there would be anywhere from 50 to 300 patients in each clinical trial, i.e., between 58,850 and 353,100 individuals putting their lives in the hands of oncology clinical trials in Canada this year. This not only effects the lives of the patients

involved, but also affects oncologists, clinicians, hematologists, project managers, pharmacists, social workers, nurses and the patients' friends and family.⁹

Table 2 Current Number of Oncology Clinical Trials in Canada

Province	Number of Oncology Clinical Trials
Alberta	158
British Columbia	62
Manitoba	94
New Brunswick	26
Newfoundland and Labrador	11
Nova Scotia	42
Ontario	510
Prince Edward Island	6
Quebec	219
Saskatchewan	49
Canadian Cancer Society (2010) ⁹	

Oncology clinical trials cost a large sum of money. The American FDA reported that a typical clinical trial consisting of phase I, II and III involving 3,330 participants can cost between \$6.6 million and \$22.1 million.¹⁰ From 2005 to 2006, the Canadian Cancer Society donated \$5.5 million to oncology clinical trials in Canada.⁹ This was followed by a \$20 million dollar donation from the National Cancer Institute (NCI) in the United States of America and industry.⁹ Funding for oncology clinical trials also comes from a large array of sources, including but not limited to organizations, individuals, physicians, medical institutions, foundations, volunteer groups, pharmaceutical companies and federal agencies. This year alone the Canadian Cancer Society is giving \$1.4 million to ten investigators across Canada in support of oncology clinical trial research.⁹ In the United States, total expenditures of the clinical trial industry have increased drastically. In 1996, total expenditures were approximately three

billion dollars, increasing to sixteen billion dollars in 2003, and twenty six billion dollars in 2007.¹⁰ Oncology clinical trials are a major part of the medical industry in Canada and the United States.

Defining and Classifying Adverse Drug Reactions (ADRs)

When a new drug is first administered to humans, sometimes the body reacts unfavorably to these novel substances, resulting in what is known as an adverse drug reaction (ADR). In order to assist clinicians and other professionals in communicating about ADRs, they are classified into five different categories (see Table 1.3 for summary). The first category, better known as “Type A” (although sometimes referred to as “Type 1”) is augmented adverse events.¹¹⁻¹⁴ These types of ADRs are most common (approximately 80 percent of all reported ADRs), and are defined as an exaggeration of a drug’s predicted pharmacological actions, a form of a toxic effect.¹¹⁻¹⁴ These types of adverse drug reactions are often reproducible and highly drug dependent.¹¹⁻¹⁴ These reactions also have high morbidity, but low mortality, rates and respond well to dose reduction.¹¹

The second ADR classification is “Type B”, (sometimes referred to as “Type 2”), “B” standing for bizarre.¹¹⁻¹⁴ These ADRs are almost the complete opposite of what one may expect from “Type A” ADRs. They are unexpected reactions that occur from the otherwise known effects of a drug, and are typically uncommon.^{11,13} These reactions are rarely dose-related and are associated with low morbidity, but high mortality, rates.¹¹⁻¹⁴ It has been found that these types of reactions are most commonly counteracted with drug withdrawal.¹¹ This does not

mean discontinuing the study of the drug, but rather discontinuing the administration of the drug to the patient experiencing a bizarre reaction.¹¹

“Type C” is the third classification of ADRs and includes reactions that are continuous or chronic.^{12,14} “Type C” reactions are uncommon and arise with prolonged drug use.^{12,14} “Type D” ADRs stands for delayed reactions, which are also uncommon and only become apparent after using the drug for quite some time.^{12,14}

The final two categories are less recognized as major classifications because they are either not directly associated with the drug or are considered a failure; they are “Type E” and “Type F”. “Type E” refers to those reactions that occur after “end of use” or withdrawal of a drug, and are relatively uncommon.¹⁴ “Type F” is a common reaction and refers to a failure of the therapy.¹³ These types of reactions may be attributed to the dose given, but are more often than not due to the drug interacting with other drugs or interventions.¹³

Table 3 Classification of Adverse Events

Type	Definition	Commonality
Type A	Augmented	Most common
Type B	Bizarre	Uncommon
Type C	Continuous/Chronic	Uncommon
Type D	Delayed	Uncommon
Type E	End of Use	Uncommon
Type F	Failure of Therapy	Common

Problems with Classifying ADRs

Although ADRs can be classified, the problem lies in actually defining what constitutes an ADR. This can become quite difficult because these definitions are very dynamic and are constantly being upgraded. Current definitions of ADRs

have become more sophisticated with time, but still remain relatively inconsistent, and many definitions lack vital components.¹⁵⁻¹⁷ For example, the World Health Organization (WHO) has used a definition of an ADR for several decades that states, *“a response to a drug that is noxious and unintended and occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function”*.¹⁵ Laurence defines an ADR as, *“A harmful or significantly unpleasant effect caused by a drug at doses intended for therapeutic effect (or prophylaxis or diagnosis) which warrants reduction of dose or withdrawal of the drug and/or foretells hazard from future administration.”*¹⁶ Health Canada reported that Canadian ADR reporting regulations define ADRs as, *“a noxious and unintended response to a drug, which occurs at any dose and requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death”*.¹⁸

The ‘standard’ definition by the WHO, as well as many definitions, can be seen as inadequate because they fail to address what can be understood as minor reactions, they do not account for error, and they tend to emphasize the ‘harmfulness’ of the event. Emphasizing the harm involved in an ADR does not sit well with patients because they may experience ADRs that do not explicitly involve tremendous physical pain (“harmful”), but none-the-less are uncomfortable and affect their well-being.^{15,16,19} ADRs are often associated with terms such as ‘death’, ‘life threatening’, ‘prolonged hospitalization’, and

'permanent disability'.²⁰ These restrictive terms need to be questioned as they fail to account for many serious ADRs.²⁰

The most inclusive definition of ADRs to date was proposed by Edwards and Aronson (2000), who stated, "*an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medical product, which predicts hazards from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product*".¹⁶

This definition is inclusive in that it accounts for minor reactions and error.

However, none of these definitions are consistent and may lack vital components, such as minor reactions and error.¹⁵⁻¹⁸ It is evident that a consensus must be reached on a standardized definition of ADRs to be used across all clinical trials, if clinical trials are to be considered a truly standardized process.¹⁵⁻²⁰

Oncology clinical trials are a long and complex process. There are numerous oncology clinical trials currently taking place in Canada, and all are run over multiple years and require numerous millions of dollars, not to mention physician, hospital, and patient time. There are also major problems in identifying and classifying adverse events, which can pose major issues in early phases of oncology clinical trials. These issues will be discussed in depth in the next sections.

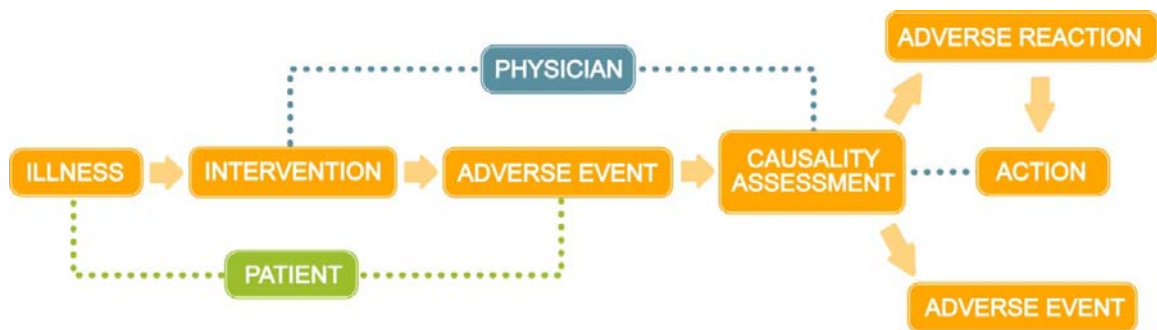
Research Study

An inclusive standardized definition of ADRs needs to be established in order to properly assign causality and maintain a level of true standardization

within the clinical trial process. Causality assessment is a process that takes place in the early phases of oncology clinical trials. It involves determining whether an adverse event (a reaction that occurs after a drug is administered) can be attributed to the drug or intervention being tested or if it is due to external causes¹⁵⁻²⁰ (see *Figure 1.2 for a summary of this process*). This diagram (Figure 1.2) was created by Cosby (personal communication, 2010) to delineate the steps that are taken to assign causality in clinical trials, and to demonstrate the patient-physician interaction during this process. First, there is an onset and diagnosis of an illness; in this case, some form of cancer. The physician then administers the drug or intervention to the patient. For example, the patient may be required to undergo chemotherapy, or is administered a drug new to the market. The patient may subsequently start to exhibit signs and symptoms of a drug's effect. Intended effects would include the reduction or elimination of disease progression, or even the eradication of the cancer from the body. Unfortunately, unintended ADRs may also occur, including, hair loss, weight loss or weight-gain, headaches, nausea etc. It is at this point when the physician must assign causality for the intended benefits and unintended ADRs of the medication. The physician needs to make a complex decision of determining whether this adverse event is due to the drug or intervention being tested, or due to an external cause, for example, the illness itself, another medication, an infection, or some unknown factor or element (such as stress, or a secondary illness not yet identified). If the adverse event is determined to be a result of the drug or intervention being tested, it is known as an adverse drug reaction. In this

case, the physician needs to determine the plan of action to be taken to deal with this ADR. If it is deemed that the adverse event was due to an external source, it remains an adverse event and no further action is taken. The process of assigning causality exists to determine a drug or intervention's level of safety, the effect it has on the body and the illness, as well as facilitating the progress of the clinical trial through to the next stages. Proper methods of causality assessment are extremely important for both the patient and to develop an overall understanding of the drug's safety.

Figure 1. The Steps in Assigning Causality



Purpose: The purpose of this study was to develop a psychosocial understanding of how clinicians assign causality in order to improve the process of oncology clinical trials. It was a qualitative based study of oncologists' views on making these decisions, with the purpose testing and verifying Figure 1. "The Steps in Assigning Causality". The research also determined if the process outlined in Figure 1 conceptualizes the process in oncology clinical trials. Lastly, the research determined what psychosocial factors affect this process, and to examined the roles that patients and physicians play in this process. The main

focus was on causality assessment and the actions taken during and after this process.

Research Question: What are the psychosocial factors that play a role in assigning causality to ADRs?

The Need for Qualitative Research

This research used a qualitative approach. A recent article published on March 12, 2010 in the Journal of Investigational New Drugs entitled, “*A Qualitative Study Evaluating Causality Attribution for Serious Adverse Events During Early Phase Oncology Clinical Trials*”,²¹ stated that this is the first study of its kind to use qualitative methods to investigate causality assessment in early phase oncology clinical trials.²¹ Qualitative inquiry within the field of clinical oncology is not a common practice, although it is in high demand. The literature that supports the rationale for this study portrays that there is a strong need for qualitative research.^{9,15-21} This is amplified by Boulton and colleagues when they stated, “the full potential of qualitative research has yet to be realized in the field of health care”.²²

A complete understanding of causality assessment in early phase oncology clinical trials cannot be understood through quantitative methods alone, and would be more appropriately investigated through qualitative methods.^{9,15-21} In order to understand the decision making process of individuals, it is imperative that a deeper understanding of the semantics of human experience is achieved.²³ This can be achieved through a psychosocial understanding of the ADR decision making process. This study will also add to the accuracy and relevance of current

and future quantitative literature surrounding causality assessment in early phase oncology clinical trials.²³ Quantitative analysis cannot address the how and why questions of human behaviour, so a holistic perspective of causality assessment cannot be reached without the use of qualitative measures.²²

Theoretical Framework

A theoretical framework is defined as the solid foundation of a research study.²⁴ A theoretical framework provides the researcher with models and concepts to guide the data analysis stage.²⁴ This research was not aimed at testing a hypothesis, but rather answering a research question, and needed a theoretical framework that supports this. “*Naturalistic Decision Making (NDM) Theory*” fits these criteria.^{24,25} It is a psychosocial theory that examines how professionals use the experience they have gained within their field of expertise to make proficient decisions within “complex real-world environments”.^{25,26} In order to understand NDM, it is important to take a look at the history of decision-making. There are essentially three separate paradigms: formal (empiricist), rationalist, and naturalistic.²⁵ The formal (empiricist) and rational paradigms are different from the naturalistic paradigm because they fail to account for the decision makers’ expertise, task complexity, as well as environmental limitations.²⁵ Therefore, formal and rational paradigms cannot be applied to real world settings.²⁵ The naturalistic paradigm however, represents a paradigm shift away from these traditional forms of thinking.²⁷ Within the field of oncology clinical trials, decisions (specifically in the form of causality assessment) are constrained by both time and uncertainty in information (for example adverse

events). Naturalistic decision-making takes these issues into consideration.^{25,27}

Unlike other decision making theories, NDM incorporates values into the decision making process, making it appealing for medical decision making.²⁸

There are five key components in Naturalistic Decision Making Research.²⁵

1. Emphasis on expert decision-making.
2. A focus on the decision making process.
3. Development of “situation-action matching decision rules”.
4. “Context bound informal modeling”.
5. “Empirical-based prescription”.

The decision making process includes; a description of the information required to make a decision, the interpretation of this information, as well as how and what rules are applied to making a decision.²⁵ The purpose of this research study is coherent with the purpose of NDM; to improve the decision making process. In order to improve causality assessment, and eliminate error, in early phase oncology clinical trials, it is imperative that an understanding of the decision making process is reached.²⁵ In doing so, this research further aims to improve decision making effectiveness, aid in developing realistic decision making strategies, and better prepare professionals making these proficient decisions.²⁵

Rationale for Research

Summary Table of Literature Supporting Current Issues in Causality Assessment

The following table (Table 4) is a summary of the relevant literature that supports the inadequacies and problems faced when assigning causality, and in doing so, provides a rationale for the research. The literature was systematically reviewed and comprised into a table format where the data is displayed in summarized form for a straightforward comparison. Experts agree that this process helps eliminate bias while strengthening the relationship between the research evidence and the study.²⁷ The relevant findings were summarized into the following categories as rationale for this study:

- Adverse Drug Reaction (ADR) reporting differs between databases and publications
- Improvements need to be made in detecting and preventing medical error; inaccurate reporting of ADRs
- Inconsistency of key terminology used to assess causality
- Inconsistent definition of harm; inter-rater probability (poor expert agreement)
- No universally accepted tool for assessing causality, need for a standardized tool
- The safety of ADR reporting needs to be revised
- There is a need to increase patient involvement in causality assessment
- Under-reporting of ADRs.

Also see Appendix 1 for the literature search parameters used to obtain these data. This table includes a description of the databases or journals searched, the search terms used, the number of original results, the criteria used for selecting and eliminating certain articles, along with a list of the chosen articles.

Table 4 Review of the Literature

See Appendix 1 for Review of the Literature Search Parameters

	Author(s)/Title/ Year of Publication	Research Question	Study Design	Relevant Findings
	Agbabiaka, T.B., Savovic J., & Ernst E. Methods for causality assessment of adverse drug reactions 2008	To review and discover the strengths and weaknesses of existing causality assessment tools.	Electronic databases were searched to find articles on existing causality assessment tools in MEDLINE, EMBASE, and the Cochrane Database including global introspection, algorithms and Bayesian tools.	-No universally accepted tool for assessing causality -Inter-rater probability (poor expert agreement)
17	Alsheikh-Ali, A. A., & Karas, R. H. Ezetimibe, and the combination of ezetimibe/simvastatin, and risk of cancer: A post marketing analysis 2009	If <i>ezetimibe</i> or ezetimide combined with simvastatin increased the risk of cancer, would cancer-related adverse events reports reflect this? In comparison to simvastatin on its own or other cholesterol-lowering drugs.	Rates of cancer in adverse event reports filed with the US Food and Drug and Administration (FDA) occurring in patients on <i>ezetimibe</i> or E/S were compared to those patients in simvastatin or other potent cholesterol-lowering drugs.	-Under-reporting of ADRS

Author(s)/Title/ Year of Publication	Research Question	Study Design	Relevant Findings
Arimone, Y., Béguad, B., Miremont-Salamé, G., Fourrier-Réglat, A., Moore, F., Molimard, M., & Haramburu, F. Agreement of expert judgment in causality assessment of adverse drug reactions 2005	To analyze and compare the judgment of 5 senior experts using global introspection about drug causation on a random set of putative ADRs. Does a group of senior experts working separately give concordant opinions in the assessment of ADRs? What are the main causes of rater disagreement?	150 drug-effect pairs were independently assessed by five experts for the probability of drug causation. Agreement among the experts was assessed using kappa coefficients.	-No universally accepted tool for assessing causality, need for a standardized tool -Inter-rater probability (poor expert agreement)
Basch, E., Jia, X., Heller, G., Barz, A., Sit, L., Fruscione, M., Appawu, M., Iasonos A., Atkinson T., Goldfarb, S., Culkin A., Kris, M. G., & Schrag, D. Adverse symptom event reporting by patients vs. clinicians: relationships with clinical outcomes 2009	How do patient and clinician reporting compare, when it comes clinical events?	Patients and clinicians independently reported 6 Cancer Institutes Common Terminology Criteria for Adverse Events (CTCAE) symptoms. A time dependent Cox regression model was used to measure associations.	-There is a need to increase patient involvement in causality assessment

Author(s)/Title/ Year of Publication	Research Question	Study Design	Relevant Findings
Béguad, B. Martin, K., Haramburu, F. Rates of spontaneous reporting if adverse drug reactions in France 2002	What is the magnitude of underreporting from serious ADRs in France from 3 different fields of pharmacoepidemiology studies?	Estimating the magnitude of underreporting by comparing ADRs to the number of cases spontaneously reported to the French pharmacovigilance system during the same period and within the same territory.	-Under-reporting of ADRs
Betancourt, B. Y., Marrero- Miragaya, M. A., Jiménez- López, G., Valenzuela-Silva, C., García-Iglesias, E., Hernández-Bernal, F., Debesa-García, F., González-López, T., Alvarez-Falcón, L., López- Saura, P., & the Cuban National Network of Pharmacoepidemiology Pharmacovigilance program to monitor adverse reactions of recombinant streptokinase in acute myocardial infarction 2005	Assess ADRs associated with intravenous recombinant SK in patients with AMI in routine clinical practice.	A spontaneous reporting based pharmacovigilance was conducted, documented and analyzed.	-Under-reporting of ADRs
Coombes, M., Mukherjee, S., Kowaleski, B., Levine, M., Cosby, J., & Arnold, A. A tool for assessing adverse	Understand the clinical reasoning behind causality assessment during phase I/II oncology clinical trials.	In-depth interviews with oncologists and trial coordinators were conducted.	-No universally accepted tool for assessing causality, need for

Author(s)/Title/ Year of Publication	Research Question	Study Design	Relevant Findings
events in phase I/II oncology clinical trials 2007 (Abstract)	Use this information to develop a causality assessment.		a standardized tool
Edwards, R., & Aronsom, J. K. Adverse drug reactions: definitions, diagnosis, and management 2000	To outline the definition of adverse drug reactions, outline their classification, and discuss ways in which they are diagnosed, managed, and monitored.	Review.	-Inconsistency of key terminology used to assess causality
Fromme, E. K., Eilers, K. M., Mori, M., Hsieh, C., & Beer, T. M. How accurate is the clinician reporting of chemotherapy adverse effects? A comparison with patient- reported symptoms from the quality-of-life questionnaire C30 2004	Are adverse events reported and assessed in chemotherapy clinical trials by clinicians accurate?	Patient reported symptoms from the European Organization for the Research and Treatment of Cancer Quality-of-Life Questionnaire C30 (QLQ-C30) were compared to clinician reporting of adverse events.	-Inaccurate reporting of ADRs

Author(s)/Title/ Year of Publication	Research Question	Study Design	Relevant Findings
Hubbard, G., Kidd, L., & Donaghy, E. Preferences for involvement in treatment decision making if patients with cancer: A review of the literature 2008	What are patients' preferences for involvement in cancer treatment decision-making?	Systematic methods were used to search for literature, inclusion (preferences for involvement in treatment decision making for cancer) and exclusion (preferences about decision making roles in cancer screening or genetic testing) criteria were applied, the quality of the studies were appraised. Relevant data from the included studies was selected and a narrative summary of this data was provided.	-There is a need to increase patient involvement in causality assessment
Ioannidis, J. P. A., & Lau, J. Completeness of safety reporting in randomized trials 2001	To scrutinize the completeness of safety reporting in randomized trials.	Survey of safety reporting in 192 randomized drug trials.	-There is a need to increase patient involvement in causality assessment -The safety of ADR reporting needs to be revised
Ioannidis J.P.A., Lau, J. Improving safety reporting from randomized trials 2002	How can we improve safety of reporting adverse events in randomized trials?	Review	ADR reporting differs between databases and publications -No universally accepted tool for assessing causality, need for

Author(s)/Title/ Year of Publication	Research Question	Study Design	Relevant Findings
Kelly W.K., & Halabi, S. Guideline for submitting adverse event reports for publication 2009	The International Society for Pharmacoepidemiology (ISPE) initiated a task force in 2004 to examine the need for guidelines in publishing AE reporting.	Literature review.	a standardized tool -ADR reporting differs between databases and publications
Koch-Weser, J., Sellers, E. M., & Zacest, R. The ambiguity of adverse drug reactions 1977	How ambiguous is adverse event reporting?	Three clinical pharmacologists independently examined 500 adverse event reports reported by physicians as ADRs.	-Inter-rater probability (poor expert agreement)
2 Mahoney, M. R., & Sargent, D. J. Adverse-event rates: Journals versus databases 2007	Is there a difference between adverse event reporting in peer reviewed publications and corresponding databases?	Using the clinical data update system (CDUS) to compare adverse event data in peer reviewed publications and adverse event data reported in US National Cancer Institute (NCI) database.	-ADR reporting differs between databases and publications -Under-reporting of ADRs
McCarthy, M. US cancer group calls for a centralized review of clinical trials 2003	This article, written from the standpoint of the American Society of Clinical Oncology (ASCO), hopes to identify and improve the standardized review process, patient safety, and public confidence in clinical trials.	ASCO calls for a review of clinical trials through a central review process, opposed to standard institutional review boards.	-Under-reporting of ADRs -The safety of ADR reporting needs to be revised

Author(s)/Title/ Year of Publication	Research Question	Study Design	Relevant Findings
Molokhia M., Tanna, S., & Bell, D. Improving reporting of adverse drug reaction: Systematic review 2009	To evaluate methods to improve ADR reporting via a systematic literature review.	Systematic review of the literature.	-No universally accepted tool for assessing causality, need for a standardized tool
Ocloo J.E. Harmed patients gaining voice: Challenging dominant perspectives in the construction of medical harm and patient safety reforms	What are the experiences of those who have been subject to medical harm?	Interviews, focus groups and surveys.	-Inconsistent definition of harm
Scharf, O., & Colevas, A. D. Adverse event reporting in publications compared with sponsor database for cancer clinical trials 2006	Does published adverse event data differ from what adverse event data is in sponsor's databases and study protocols of data collection requirements?	This study compared studies that used a common toxicity criterion. Study protocols for reporting adverse event data were compared to methods cited in publications. Adverse event reports in these publications were then compared to adverse event reports in the trials' databases.	-ADR reporting differs between databases and publications Inter-rater probability (poor expert agreement)
Trotti, A., Bentzen, S. The need for adverse effects reporting standards in oncology clinical trials 2004	Prove the need for reporting standards in oncology clinical trials.	Review	-No universally accepted tool for assessing causality, need for a standardized tool

Author(s)/Title/ Year of Publication	Research Question	Study Design	Relevant Findings
Westwood M., Rodgers M., & Sowden A. Patient safety: Mapping the literature 2002	What have been the goals of patient safety research? What methods have been used inpatient safety research? What types of studies have shown what kind of results?	A mapping exercise of the literature on patient safety was performed using 15 databases	Improvements need to be made in detecting and preventing medical error

Rationale for Research Continued

The following sections will address, in more detail, the major issues with ADRs and causality assessment that were outlined in the literature and summarized in Table 4.

The Definition of Harm

There are significant differences between patients' and clinicians' perspective on harm, which contribute to the variances in adverse event reporting between these individuals. There is great ambiguity with the term harm in any circumstance. Harm is a loaded term and can include physical, emotional, psychological, social, and economic factors.²⁹ Harm is both objective and subjective, but is all too often associated with objectivity within the medical field.^{19,29} According to Ocloo (2010), "*The process of defining medical harm is not value free, but it tends to reflect a narrow clinical interpretation of harm that excludes non-clinical or non-disease specific outcomes that the patient may consider harmful.*".¹⁹ In clinical trials, it is the patients who are exposed to harm, so the definition of harm needs to be more patient centered.¹⁹ The purpose of the research was to come to a psychosocial understanding how clinicians decide which adverse events are harmful and which events are not. Through this, a better understanding of the differences between a patient's and a clinician's definition of harm can be met. A psychosocial understanding can aid in ensuring that the codes and guidelines involved in clinical trials maintain a strong inclusive definition of harm, which will later aid in creating more accurate risk-benefit ratio, keeping patients safe from harm.²⁹

Seeing that patients and professionals disagree on the definition of harm, there can also be a large variance between what patients and professionals report when it comes to adverse events. Although patient reporting is not currently a standard practice in assessing causality of adverse events in oncology clinical trials, research has shown it can be quite complementary.³⁰ Patient reporting of ADRs is much different than what is reported by professionals; patients typically focus on the minute adverse events, ones that fluctuate on a day to day basis, whereas professionals tend to place the emphasis on more severe adverse events that are likely to have a strong impact on the clinical trial.³⁰ Since current methods do not incorporate the patient's perspective, they do not include the events that affect the patient's daily health.³¹ Evidence suggests that by including the patient in the reporting process, a more complete picture of drug safety can be established.³¹ Looking at this through a critical lens, it may be proposed that patient reporting is subject to bias and error; however, Basch et al. (2009) argue that professional reporting is biased as well.³¹ When it comes to patients, the majority prefer to be highly involved in any aspect of treatment as well as decision-making.³⁰ Therefore, not only would patient involvement aid in causality assessment, it will also allow patients to feel more confident in clinical trials. Through a psychosocial understanding of how clinicians assign causality, an understanding of the role patients play in the process can also be met. It is evident that patients do not play a strong enough role in the causality assessment process, which may contribute to the difficulties of professionals' experiences.

In any field of research, it is critical that there is consistency amongst its professionals. However, Airmone et al. (2005) compared adverse event reporting rates through global introspection of five senior experts and found that agreement between experts was poor.³² Experts indicated it was difficult to reach an agreement while working separately without the use of a standardized procedure.³² This is not new; Koch-Weser, Seller and Zacest published a study in 1977 that reported similar findings.³¹ Using NDM, it is possible to develop a psychosocial understanding of how clinicians assign causality, the tools they use, and the challenges they face, which will aid in creating consistency in professionals' reporting. By understanding how individual clinicians make these decisions, links between professionals' decision making can be made.

Time Constraints

Time constraints also influence causality assessment and adverse event reporting. Often, oncology clinical trials are time dependent due to drug development costs and federal regulations. Experts have reported that time restraints place added pressure on clinicians and significantly contribute to the under-reporting of adverse events.³³⁻³⁵ It has also been reported that time restraints serve as barriers to other aspects of clinical trials including office visits, recruitment and assessment of health related quality of life.³⁶ Minor and one-time reactions often take up too much valuable time in the clinical trial process, and therefore, are often left under-reported. Time restraints can also reduce the quality of decision-making and the confidence in these decisions by clinicians.^{33,34} This is a major issue in clinical trials, and it is absolutely crucial that

this issue is prominently addressed. Clinical trials put patients' lives at risk, so it is very problematic when clinicians are not confident in their decision-making abilities, or feel rushed while making these important decisions. Any 'short cutting' and under-reporting may benefit drug development costs and pharmaceutical companies, but it clearly will not provide a true reflection of the drug's ability and effects, nor does it reflect the patients' and professionals' best interests.³³⁻³⁵ Given the time constraints placed on clinicians, it can be expected that errors will be made. A quote taken from Cosby's 2010 report exhibits this phenomenon; *"the culture of medicine creates an expectation of perfection and attributes errors to carelessness or incompetence"*.³⁷ The system is often the cause for these time pressures, but because the clinical trial system is viewed as 'perfect', it can be very difficult to explore decision making. It is evident that time pressures affect clinicians' decision making skills, but the research's purpose is to understand to what extent, how, and why this happens.

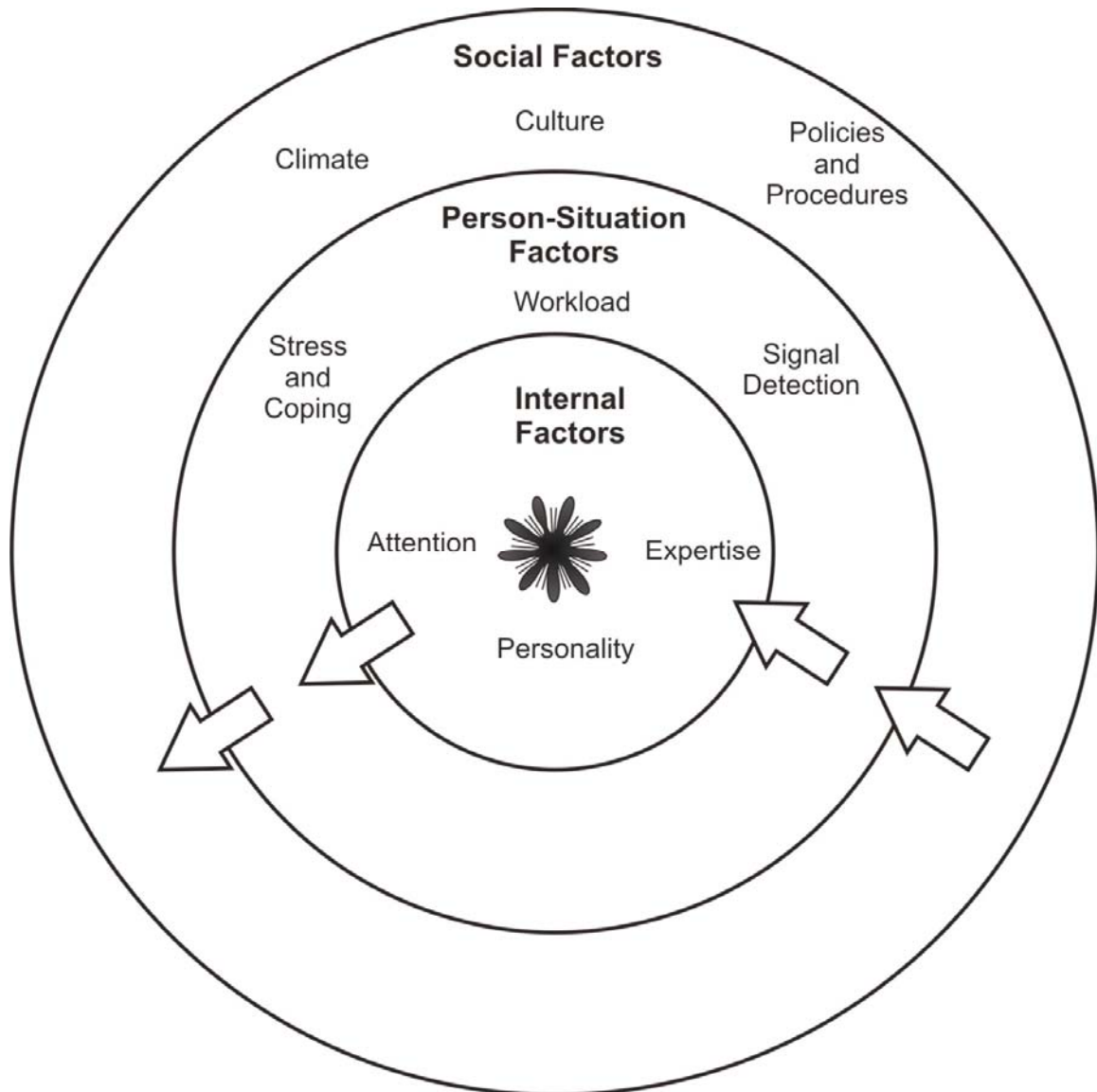
Constraints of Error Reporting Systems

The use of language plays a key role in defining and preventing medical error. In a study by Elder, Palleria, and Regan (2006), it was found that the definition of medical error is inconsistent, particularly between what patients and physicians define as medical error.^{38,39} A paper released by the Institute of Medicine in 1999 entitled, *To Err is Human: Building a Safer Health System*, defines medical error as *"the failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim"*.⁴⁰ Errors can start small as difficulties in practice, interventions and products, and develop into system

errors.⁴⁰ Most medical errors are actually the result of a system error, but are still primarily viewed by physicians as individual errors.^{40,41} This can contribute to the under-reporting of medical errors because individuals feel that they may be held liable for the error.³⁷ A diagram by Rickles and colleagues (2010), illustrates how systems errors are actually a combination of many factors (See figure 2.).⁴¹ The chance of making an error is present in medical decision making, and this is clearly outlined by the NDM model which recognizes that these decisions take place in a complex real-world environment and that these decisions are often constrained by time and uncertainty of information.^{25,27} The aim of the research is to understand this fear of medical error through NDM and the psychosocial elements that coincide with it.

System errors have a major impact on patient safety. In fact, it is estimated that medical errors are the eighth leading cause of death in the United States of America and that the American health care system is the third leading cause of death in the United States, right behind cancer and heart disease.^{40,42,43} A startling 106,000 Americans die each year from adverse drug reactions alone.⁴³ The deaths are the result of normal doses, known effects, and proper administration; this number is more than doubled when medical error is taken into account. It was also found that Americans expressed great concern about the risk of medical error and were open to both public and private investigation to reduce the risk of medical errors.⁴² Americans are right to express the concern considering the Institute of Medicine estimated that more than half of adverse events are a result of preventable medical errors.⁴⁰

Figure 2. A Multilevel Framework of Influences on Error Occurrence in Organizations Systems.⁴¹



As evident, there is plenty of room for improvement when it comes to medical errors and a systematic change is needed.^{41,44} Drastic measures do not have to be taken; in fact, large improvements can be made with simple interventions. Examples include clinical support systems, patient monitoring and reminder systems.^{40,42,43} These little steps will have an enormous impact on medical errors and in turn improve patient safety. Other more drastic solutions include a nationwide error reporting system, which would aid in creating an active and standardized method of error reporting.³⁷ Clinicians face many issues when assigning causality and have many concerns. It can be argued that this decision making process is full of imperfections, and errors are inevitable. Language and under-reporting of medical errors are serious issues that need to be addressed within the field of oncology clinical trials. A naturalistic decision making perspective of causality assessment can help to understand and prevent medical errors.

Under Reporting of Adverse Events

Medical errors are often severely under-reported in oncology clinical trials.^{45,46} Unfortunately, 'under-reporting' has no standard definition, but there are several proposed definitions of under-reporting.⁴⁶ For example, it could be that the percentage of the number of the ADRs reported does not match those that are suspected.⁴⁷ Several studies have been performed to explore the under-reporting of adverse-events in clinical trials. Alsheiki-Ali and Karas (2009) compared the rates of adverse event reporting between two drugs.⁴⁸ The first drug was *ezetimibe* and the second was *ezetimibe* combined with *simvastatin*,

which is currently known to increase the risk of cancer.⁴⁸ The study found that adverse event reporting between the two drugs did not reflect that one drug increased the risk of cancer over the other and concluded that adverse events are widely under-reported.⁴⁸ Bégaud et al. (2010) compared the rates of adverse event reporting using three different perspectives of pharmacoepidemiology in France: general practitioners, inpatients, and medical departments.⁴⁹ The study found that on average, less than five percent of all serious ADRs are actually reported, leading to the conclusion that adverse event under-reporting is a serious issue.⁴⁹ Mahoney and Sargent (2007) compared rates of adverse event reports of peer-reviewed publications to their corresponding databases.⁵⁰ The study found that there was not only an under-reporting of serious adverse events, but also of minor and reoccurring adverse events.⁵⁰

The prevalence of under-reporting can be attributed to a variety of reasons, the first and foremost being that adverse events are reported on a voluntary basis.⁵¹ This being said, it is not mandatory that all events are reported, but that only those that are seen as serious, rare, and attributable to the drug being tested, leaving out minor and reoccurring events.^{50,51} Under-reporting can also be attributed to the fact that physicians fear being individually blamed for systematic errors.^{40,41}

“Lippincott’s Guide to Preventing Medication Errors”, a nursing text published in 2003, states that reports are to be made if the drug being tested is responsible for: “death; life-threatening illness; initial or prolonged hospitalization; disability; congenital anomaly; need for medical or surgical intervention to prevent

a permanent impairment or injury".⁵² Again, this does not include minor and reoccurring events. This book also includes a section on "*Your responsibility in reporting*", in which it states: "*When filling out a MedWatch form, keep in mind that you are not expected to establish a connection between product and the problem. You do not have to include a lot of details; you only have to report the adverse event or the problem with the drug or product.*".⁵¹ This lack of detail is a major issue in under-reporting.

Under reporting can also be attributed to researcher bias; inconsistency in reporting standards and classification methods; incomplete and over simplistic reports; lack of proper training by personnel who complete the reports; and lack of awareness.^{51,52} As well, there is usually a gradual decrease in reporting over time once a drug has been introduced; therefore, it is likely that new drugs will have higher rates of adverse event reporting than older drugs.^{53,54}

It is also necessary to consider the external reasons for under-reporting, such as business rules and regulations set forth by databases, as well as publicity.^{50,55} Businesses sometimes have very specific rules that skew the reporting of adverse events, such as not accepting reports that contain incomplete or queried information, not accepting reports that make note of ADRs that occur during non-treatment phases, as well as not accepting "*incomplete data mappings*".⁵⁰ Therefore, if databases refuse to accept these sorts of information, it is likely they will never be reported in the first place. There are also influential differences between adverse events reported in databases and their respected publications, as reported by Kelly and colleagues in 2007, who found

that very little to no requirements are established in order to publish adverse events and propose that standardized guidelines be established.⁵⁶

The high incidence of under-reporting of adverse events leads to inaccurate findings and has strong implications on many aspects of clinical trials.^{53,57} The first and most pressing implication is patient safety.^{48,51} When adverse events are under-reported, patients may be exposed to drug-induced harm because risk-benefit ratios are not accurate, affecting patients' quality of life, morbidity and even mortality.^{33,57} This can lead to patients being administered toxic dosages of a drug or even exposure to a drug that should be withdrawn from the trial. Other implications include an ill effect of standardized review processes, public faith and trust in clinical trials, and financial drain on the health care system.^{16,33} The purpose of the research is to exemplify this need for standardized reporting procedures. It is hoped that with the aid of NDM, the research can actually explain why underreporting is an issue clinicians struggle with, and will propose reasonable solutions.

There are many issues associated with reporting adverse events, including an inconsistent definition of harm, constraints placed on professionals and severe under-reporting, all which can be understood and addressed through a NSM perspective. However, reporting adverse events is only the first part of the process, and is followed by the difficult decision of determining whether or not the adverse event can be attributable to the drug or intervention being tested.

Current Tools for Assessing Causality

There are three primary types of tools used for assessing causality of adverse events in oncology clinical trials; global introspection or expert judgment, Bayesian approaches, and operational algorithms.⁵⁸ Each of the methods utilizes different causality categories, and therefore, uses different criteria to assess causality. The outcome of an undefined categorical approach delivers great inconsistency between methods.⁵⁸ Although some methods are more commonly used over others, no single method of assessing causality has been universally accepted.⁵⁸⁻⁶²

Global Introspection

Global introspection is the most common tool used to assess causality of adverse events due to its simplicity.⁵⁹ This approach does not involve a standardized tool, but rather uses prior knowledge and experiences to assess causality on an individual basis.⁵⁹ This method has gained popularity because it is very similar to clinical diagnosis, a common practice within the field of oncology, and is therefore seen as a more familiar and logical way of providing assessment.⁵⁹ However, although it is relatively easy to use, this method has been criticized. Due to its subjectivity, it falls short of reproducibility standards due to the preconceived notions and background experience of the professionals using this tool.^{59,60} This often leads to missed or misinterpreted information; consequently the validity of this method is strongly challenged.^{59,60}

Bayesian Approach

The Bayesian approach addresses probability from the standpoint of a medical equation.⁶² The method involves assigning 'prior probability' to an adverse reaction. To do this, prior probability is calculated from the pre-marketing information of the clinical trial along with prior epidemiological information.^{59,60,62} This information is then used to create a 'posterior estimate of probability' by taking into account new information presented by the individual case, which in a sense provides a revised estimation of causality.^{59,60,62} The Bayesian approach is considered the most valid tool for assessing causality; however, it lacks popularity due to the complicated and involved mathematics.^{59,60,62} This method also presents challenges because the information needed to determine prior probability is often difficult to obtain.^{59,60} This information is often withheld from the scientific community due to confidentiality agreements between pharmaceutical companies and regulatory authorities.⁶⁰ It is also important to note that even if access to this data is granted, there are often inconsistencies with the way the information is formatted, preventing its relevant usage in Bayesian approaches.⁶⁰ Using such quantitative methods of assessment also distances the patients and limits their involvement in the clinical trials process.

Algorithms

Algorithms assess causality of adverse events through operational methods.⁶² They typically consist of a series of questions, but can range anywhere from a non-scoring flow-chart to a long list of detailed questions that require heavy computer analysis.⁶⁰ These methods are seen as advantageous

because they are transparent and have relatively high consistency rates.⁶⁰

However, these methods also hold disadvantages, in that they are relatively inflexible.⁶⁰ The structure of algorithms is highly criterion dependent, lacks clinical judgment, and the use of external information.^{59,60,62}

By identifying which approach (global introspection, Bayesian, or algorithms) the participants currently use, a better understanding of the social and psychological elements that play a role in the decision making process regarding that specific tool, can be met. This can add to the current literature surrounding the strengths and weaknesses of the various tools developed to aid in causality assessment.

Lack of a Standardized Method for Assessing Causality

It would make sense to assume that since there is inconsistency amongst professionals, inconsistency between professionals and patients, along with severe under-reporting of ADRs, that there is no accepted standardized procedure of assessing causality. Several studies have addressed these issues and expressed the need for a standardized procedure.^{59,60,62} In order to move forward and improve the safety of patients in clinical trials, it is critical that a standardized method for reporting adverse events be established.⁶² Airmone et al. (2005) indicated that it is extremely difficult for professionals, who are considered experts in the field, to make coherent judgments of causality.³² When these individuals are working independently, it is near impossible for them to make consistent conclusions of causality without using a standardized tool.³²

Ioannidis and Lau reviewed the completeness of safety reporting in clinical trials and had some findings of concern.³⁴ 192 clinical trials were reviewed, and out of that 192, over sixty percent of safety reporting was found to be inadequate and often times neglected.³⁴ This review also indicated that key information would often be absent in the reports. For example, adverse events would be reported without a level of severity indicated.¹⁴ There is a strong need to develop a standardized tool.

Coombes et al. (2007) indicated the need for a standardized tool for assessing causality, as expressed by their participants.⁶⁰ This study conducted interviews with oncologists and clinical trial specialists to find that, although these professionals used a logical system of reasoning when assessing causality, they still acknowledged many challenges and barriers to this process.⁵⁹ The main challenge indicated by participants was the poor quality of information resources.⁵⁹ There is a pressing need to highlight the importance and need of a standardized tool, as causality has a strong impact on intervention development, and patient safety.⁵⁹ As Trotti and Bentzen (2004) clearly state, when it comes to a standardized tool, “the only harm is not trying”.⁶³ The purpose of the research is to understand the tools clinicians use, and their likes and dislikes of those tools. Through a psychosocial understanding of causality assessment, the creation of a standardized tool is possible.

Methodology

The study employed an interpretive-descriptive research design, i.e., the study was explorative in nature, and used the participants' words and experiences as the primary means of data explication and interpretation.⁶⁴

Research Paradigm

The research was centered on an interpretive worldview. The emphasis of the research was on the decision making process, more so than causality assessment outcomes. The research was concerned with interpreting and understanding the unique decision making experiences of these clinicians and clinical trials specialists.^{64,66,67}

Phenomenology

This study assumed a phenomenological orientation; its purpose was to study adverse events reporting from a clinician's point of view, a very emic approach.⁶⁸ According to Creswell (2007), a phenomenological approach is best suited for this study because the purpose is to understand various clinicians' experiences within oncology clinical trials. It is important to understand these experiences in order to improve the administration of clinical trials.

Edmund Husserl introduced the concept of phenomenology in the early twentieth century.⁶⁶ Husserl believed that certainty is possible within one's own consciousness, focusing on the lived experience of a particular phenomenon.⁶⁶ Other key historians in phenomenological research are Maurice Merleau-Ponty and Michael Polanyi.⁶⁶ Merleau-Ponty and Polanyi proclaim that in phenomenological research, it is impossible to separate one's experiences from

the world they live in. Maykut & Morehouse (1994) also established that the world is understood through multiple realities.⁶⁶ Phenomenology is therefore a methodology of choice for this study because its purpose is to understand the experience of clinical trials through the multitude of experiences and perspectives shaped by the world in which the clinicians make decisions, and their perceptions of that world. The focus of this research was on Husserl's work in which the emphasis was on how phenomena arise through lived experience.⁶⁶ The emphasis was on understanding how clinicians experience decision making, in a clinical trial setting through conscious acts.

Phenomenology is also consistent with an interpretive worldview. In phenomenological research, the researcher can never detach him/herself from whatever it is that is being studied, they are always going to have some sort of presupposition to the data.⁶⁸ The purpose of the research was to gather information regarding the perspective of clinicians about the phenomenon of causality assessment. Phenomenology recognizes that the experiences of these clinicians will be interpreted by the researcher, acknowledging that the researcher's own predispositions will be part of this process.

The purpose of using phenomenological methods for this study was twofold. First, to improve our understanding of causality assessment and make these subjective experiences known and intelligible.⁶⁹ Second, to find meaning in the shared experiences of these clinicians.⁶⁹ Phenomenology was well suited for this study because its purpose is to understand several individuals' common or shared experiences of adverse event reporting and causality assessment.⁶⁶

Data Collection

This study analyzed data from Mukherjee and colleagues' 2010 research paper entitled *A Qualitative Study Evaluating Causality Attribution for Serious Adverse Events During Early Phase Oncology Clinical Trials*.{Mukherjee, 2010 #20} The data were collected with the intent of development a causality assessment tool to be used in oncology clinical trials. According to Osborne (1994), phenomenology based interviews are an ideal way to collect introspective reports, giving the researcher an opportunity to understand participants feelings.⁶⁹ Thirty two individual face-to-face interviews were conducted in a private manner between the dates of May 1st, 2006 and August 31st, 2006. After participant permission had been granted, the interviews were digitally recorded, and hand written field notes were also taken during the interviews.²⁰ All interviews were conducted in English by an internal researcher trained in qualitative interview methods. The average interview was thirty five minutes in length, but ranged anywhere from twenty five to fifty minutes.²⁰ Interviews were preformed with the assistance of a semi-structured interview guide, consisting of open-ended questions, developed by the research team along with the support of two external researchers. The interview guide was first piloted at the Juravinski Cancer Centre in Hamilton, Ontario to ensure appropriateness and clarity. (See Appendix 2: Interview Guide). Transcripts of these interviews were then verified, and an executive summary of the interview data was sent out to all participants for verification.

Participants

Five Canadian academic cancer centres along with the National Cancer Institute of Canada's Clinical Trial Group (NCIC CTG) were used as recruitment sites. Purposeful sampling was employed to maximize geographical and organizational variations between participants.²⁰ Key informants were located through the NCIC CTG Investigational New Drug (IND) committee. Participants experienced in early phase oncology clinical trials were selected. These professionals included medical oncologists, hematologists, and clinical trial coordinators. These participants had a range of experiences within oncology clinical trial settings, large scale randomized controlled trials, as well as industry and non-industry supported trials.²⁰ A letter of invitation (See Appendix 3) was sent out by Andrew Arnold, and this was followed up by a phone call one week later by the study-coordinator (Megan E. Coombes). The participation rate in the study was sixty five percent, resulting in a total of thirty two participants whose characteristics are summarized in the table below.²⁰

Table 5 Characteristics of Participants

Characteristic	N = 32
Gender, <i>n</i> (%)	
• Female	16 (50)
• Male	16 (50)
Centre, <i>n</i> (%)	
• BC Cancer Research Centre (Vancouver, BC)	6 (19)
• Juravinski Cancer Centre (Hamilton, ON)	10 (31)
• London Regional Cancer Centre	5 (16)
• Ottawa Regional Cancer Centre	9 (28)
• Kingston Regional Cancer Centre	1 (3)
• NCIC (Kingston, ON)	1 (3)
Professional Group, <i>n</i> (%)	
• Medical Oncologist/Hematologist	21 (66)
• Clinical Trial Coordinator (CTC)	11 (34)
Years as a clinical trial researcher (yrs), <i>n</i> (%)	
• < 5	5 (16)
• 5 – 10	13 (42)
• > 10	13 (42)

Researcher's Role

In this study, as in all qualitative studies, the researcher plays a critical role in the research process. In qualitative research, the researcher is the primary research instrument used to collect and analyze data, and plays a very active role in the research process.^{70,71} Due to the fact that qualitative researchers play such an active role in the research, power relations are often formed in these settings.⁷² A set of experienced professionals with knowledge of the subject area, including an internal researcher with specific training in qualitative interviews and research methods conducted these interviews. The researchers made the purpose of the study clear and concise, and reassured the participants of their

valued contribution to this study. The research reported herein represents a secondary analysis of the data obtained by these researchers.

It is very important for the researcher to take a subjective role when engaging in research.⁷² The researcher's cognitive and affective subjectivity are critical in qualitative research. This subjectivity creates empathy within the study and allows the researcher to enter the world of the participant and gain an understanding of their perspectives.

Explication of the Data

Groenewald (2004) emphasizes the use of the term 'explication of data' over data analysis due to the dangerous implications that analysis can have on a phenomenological study.⁶⁸ The term 'analysis' implies breaking something down into bits and pieces, and if this were the case, within a phenomenological study, the phenomenon as a whole might be lost.⁶⁸ On the other hand, explication of the data implies that the phenomenon will remain in its entirety, but the various elements of the phenomenon will be revealed.⁶⁸

In order to analyze a phenomenological study, researchers suggest the following steps: transcribing any materials necessary, using bracketing activities and phenomenological reduction, gathering a sense of the whole, delineating meaning units, clustering meanings units and forming themes, summarizing, and creating a composite summary.^{66,68,73} These transcripts were analyzed in chronological order with respect to the order the interviews were conducted.

The first stage of data explication involved transcribing any necessary components.⁷² However, for the purposes of this study, a secondary data

explication of pre-transcribed interviews was performed. The next stage in data explication was bracketing and phenomenological reduction.^{68,74} Bracketing involves, in the most literal sense, bracketing out the researcher's preconceptions toward the phenomena being studied.^{64,75,76} Bracketing is particularly important in instances where the researcher has had experiences with the phenomena being studied, although this is not the case for this study. However, bracketing not only involves setting aside personal experiences, but also setting aside common sense, scientific foreknowledge and empirical data.⁷² This allows the researcher to enter the unique lifeworld of the interviewee and gain a true essence of the phenomena without being bound by prejudice.⁷² (Please see Appendix 4 for Bracketing Activity.) Phenomenological reduction was achieved by looking through the interview transcripts, field notes and relevant documentation. The data were read repeatedly until the meaning started to emerge on its own and a holistic sense of the data was obtained.^{72,77,78} At this point, the researcher left the world of the researcher, and entered the world of the interviewee. The focus was on the meaning that was actually presenting itself. The researcher did not look for certain aspects of the phenomenon, but was open to the data and just let the meaning naturally occur.⁷² Once phenomenological reduction took place, a holistic sense of the data was gathered. This involved looking into all aspects of the data, and making more detailed notes on the intuitions that emerge along with reflexive notes.⁷² The purpose of this stage was to gather a holistic sense of what the data were portraying by staying as true as possible to the meaning derived from the participants' experiences in clinical trials.⁷²

After a holistic sense of the data was established, meaning units were then delineated. This involved picking out statements, quotes or sentences that brought meaning to the phenomenon through a process known as horizontalization.⁶⁷ Horizontalization aims to highlight data that help us understand how the interviewees experience the causality assessment.⁶⁶ This is very similar to the process of meaning coding, in which the researcher will attach key words to represent a statement, making the statement easily identifiable.⁷² In the same manner, delineating meaning units involved creating a list of unique and redundant meanings, relevant to the meaning the researcher extracted from the data.^{68,74} To do this, the researcher kept track of the number of times a unit of meaning was mentioned in order to determine its significance.⁷⁷

The next stage of data explication involved clustering meaning units and forming themes. This stage is very similar to categorizing codes presented by Kvale and Brinkmann (2009), in which the researcher looks for meaning units that naturally group together with other meaning units to form a theme.⁷² A true sense of the essence of the clusters and the meanings they hold was established, and themes were developed to form an accurate representation of these meanings.⁷² (Please see Appendix 5: “Clustering Meaning Units Into Themes.”)

These themes were then used to create a “textural description” of what the interviewees experienced in their decision making process, including “imaginative variation/structural description” (the context in which they experienced it).⁶⁴ These textural and structural descriptions were then used to construct an

“invariant structure”, which is an amalgamated description that represents the essence of the phenomenon.⁶⁷ A summary was then created that incorporated all themes, both those that are unique and those that are redundant, across all collected data, serving as the findings section of this thesis.⁷²

Trustworthiness

Triangulation was used to come to a deeper understanding of the phenomenon by combining methods for more robust results. In this particular study, analyst triangulation methods were employed. This form of triangulation consists of using different parties to analyze data.^{79,80} Analyst triangulation reduces selective perception and reveals insight that might not otherwise be revealed through a single analyst approach.^{79,80} This study meets analyst triangulation by using three separate approaches. The interview data were first confirmed through member checking in the primary study, followed by data analysis by a qualitative research team, in order to develop a tool for assigning causality. This study then took a third approach by analyzing the interview content through a psychosocial approach known as naturalistic decision making.^{24,25} The researcher was completely removed from the data, as she was not a part of the original study, nor invested in the grant-in-aid. This distance from the original study further validates the use of analyst triangulation. The aim of analyst triangulation is not to meet a general consensus on an interpretation of the data, but rather to understand multiple perspectives.^{79,80}

Skeptical peer reviewing was also used to obtain trustworthiness within the study.⁸¹ My supervisor, as well as the rest of my committee served as

skeptical peer reviewers. They vigorously assessed the methods, meanings, and interpretations of this study.

Bracketing activities were also performed by the researcher, prior to data analysis, to further ensure trustworthiness of the findings (See Appendix 4: Bracketing). This involved having the researcher set aside all foreknowledge and predispositions toward the phenomenon being studied in order to be fully open to the natural meaning within the experiences of these participants.

Findings

The purpose of this study was to develop a psychosocial understanding of how clinicians assign causality. Using a NDM perspective, an emphasis was placed on expert-decision making. Through the descriptions of the participants' experiences, five themes were discovered:

- There were insufficient resources to support the decisions being made
- Assigning causality is a task full of uncertainty
- The process of assigning causality was full of subjective judgments
- There was an apprehensive attitude towards causality attributions
- There were competing goals between investigators and drug companies as well as investigators and their patients.

Each main theme was comprised of several subthemes (please see Appendix 5: Findings Summary Table). Each one of these subthemes followed a particular pattern that

1. Identified a grey or problem area
2. Identified a strategy for coping with the issue

3. Provided a description of the potential consequences that may result from these problem areas.

These themes serve to answer the original research questions of how these professionals use the experience they have gained and what psychosocial factors play a role in assigning causality. This extensive quote demonstrates the complexity of causality attributions and serves as an excellent summary of this study's findings.

And I think a lot of things can happen under the, under the banner of uncertainty. You know, you can be forced to under, I think that uncertainty is at the heart of this, its at the heart of this. And I don't think it's a matter of honesty or dishonesty, I think it's uncertainty and how do people cope with uncertainty? And I think that this actually is the measure of whether enterprises succeed or fail. You know, it's how they deal with uncertainty. So I think for example one of the differences between successful businessmen and unsuccessful people in business is that the unsuccessful people don't know how to deal with uncertainty. Um, because life is full of uncertainty and you know, it's possible to be panicked into, into making a wrong decision. On the other hand it's also possible to be paralyzed into not making any decision at all. [yeah] So when you see these kind of little human dramas played out in this situation as well because, but I think it's a mistake to not allow the physician to be uncertain when he or she is genuinely uncertain.- S22

Insufficient Resources

No Training

The subjective nature of causality assessment in early phase oncology clinical trials stems from the lack of resources available to assist professionals in making these decisions. To begin, these professionals are given very little to no training on how to assign causality. A few interviewees mentioned that the pharmaceutical sponsors had training modules on adverse event reporting, but nothing related to causality assessment. Others have mentioned that

occasionally, in start up meetings, a small 'blurb' will be given on assigning causality. However, all of these experts agree that there really has not been any formal training.

There hasn't been any formal training, yeah, there's hasn't been anything formal.- S05

I've had no formal training [no] actually.- S11

There's no formal training really, you just kind of got thrown into the position.- S32

Without formal training, there are always going to be inconsistencies in reporting standards, which is evidently still a major issue in oncology clinical trials. These professionals cope with little to no training through on the job experience, whether it is self-training or training one another as they go. It has been described as a trial and error process.

Trial and error I guess. I mean the only, the only lecture I've ever heard about is, I've heard A speak once, but other than that you know, really nothing. I mean you'd ask other more senior investigators what they would say for this particular event and so on. But otherwise, there was no formal training.- S26

The Lack/Need of an Assessment Tool

When asked if there were any tools to aid clinicians in assigning causality, no one could generate a response. The only answer seemed to be "no". In fact when asked this question, one interviewee responded, "*Are there any tools out there?*"- S18. This statement exemplifies that the causality assessment tools are not made widely known to professionals. From the various flowcharts, algorithms, decision-making trees, and Bayesian approaches available, not one

interviewee could identify a tool. There is not a universally accepted tool, and in most cases, these professionals do not use a variety of tools at their disposal.

So there's often not a lot of guidance it's more winging it.- S01

Clinicians did agree that a tool would be useful. A tool would aid in promoting consistent causality attributions between professionals. In order to cope with not having a tool to make these decisions, these professionals did state that occasionally they would work through the history and strength of the association (between the adverse event and drug administration) to make a decision. Some clinicians considered the investigator brochure as the closest thing to a tool they could think of, but indicated that they mostly use the brochure to better understand some of the toxicities.

None. [no] No, well I mean, I guess I shouldn't say that, none in terms of standardized criteria that's for sure. Resources, unless you mean basically going back to see maybe the investigator brochure and trying to understand some of the toxicities.- S13

...Well you can look first at the investigators brochure, you, that, that's what you're supposed to look at...- S08

Lack of Resources

With no tools being used, it is not unimaginable to assume that these professionals are lacking other resources as well. Physicians explained their need for more detailed information.

Yeah, more detailed information I guess, other than what's in the consent form, having a list of expected events and maybe, some of them put in the percentages of what the patients have already experienced. So yeah, I guess that, just a more detailed sort of, um, like I was saying we go to the dose modification and it will list sort of what the expected toxicities are and the rules to follow. So maybe to have some kind of I don't know, chart or information in that area to go to, to see what we're looking for and how they expect us to assign the causality.- S25

The consent form is an excellent start, as it has a list of expected events, and in some cases, the percentages of events that the patients have already experienced, but these often lack other supportive information, such as, dose modification; a listing of expected toxicities, and rules to follow. There is still no information as to what the expectations are in terms of standard practice on how to assign causality.

Lack of appropriate information.- S06

This leads to unconfident decisions being made by these professionals. In order to cope with the lack of resources available to them, these professionals rely heavily on the experience they have gained within their field to make proficient decisions.

So it's more on a, just based on the experience of taking part in the study and the hunch factor. I don't actually have a tool that I use, so I think something like this would be very handy.- S10

Vague Definitions

Often times, the definitions of various causality assessment terminologies, are vague. For instance, although these professionals will be asked to identify whether the adverse event is certain, probable, possible, unlikely, there is no definitions of what these terms mean in relation to causality assessment. Some interviewees even felt that sponsors make the wording vague on purpose.

Well, most of my studies are also sponsor studies and they tend to make the wording vague on purpose. [laughter] Probable, possible [the wording of what] probable, possible, definitely related, possibly related all the, so sometimes that can be a challenge if it's something you haven't encountered before.- S28

This is challenging to professionals, especially if they have never encountered these terms before. It is really, as one interviewee puts it, an “imprecise science”- S08, and it becomes extremely difficult to be certain in one’s attribution. In order to cope with the lack of standardized definitions, these professionals rely on their experience to assign causality.

I mean it’s almost from the experience we’ve had with drugs.- S03

So I think, those ones are okay because you’re basing it a bit on personal experience [yeah] and a little bit on what’s published.- S04

Basically all one can really do is, based on experience of managing these people sort of know what to expect as their cancers progress and as their regional stages of life, as in previous experience in managing.- S06

Communication Issues and the Role of the Physician

There are also communication issues that arise when assigning causality. One of the main gaps in communication seems to occur between the interviewees and their sponsors. For instance, the interviewees often had questions about a certain adverse event, but found it difficult to access information that would allow them come to a better understanding of the drug’s pharmacology, beyond the investigator’s brochure. Even when writing up reports, interviewees felt that it would be helpful to know more about the sponsor’s data management. It would help them to understand their role, and understand how companies try to collate the information they send to them. This lack of communication makes it extremely difficult to come to a unanimous decision.

Well usually there’s teleconferences and other meetings to discuss what’s happening with other patients. But a lot of times communication isn’t as good as it could be.- S07

Interviewees also felt like sometimes they had no idea what other investigators were doing. Having the opportunity to discuss these issues, on a regular basis, with other investigators would aid in filling this communication gap, and lead to more unanimous decisions. Physicians cope with the lack of communication with their sponsors by searching for additional resources online, and by consulting with other physicians.

Another communication lapse lies between the physicians and the patients. Physicians felt that, at times, that they do not get all the information they need from a patient. In order to narrow this communication gap, these professionals cope by getting to know their patients. By coming to a better understanding of the patient's personality and outlook on the trial, both of which are very subjective, one is better equipped to make more informed decisions when assigning causality. This can also help eliminate the inaccurate representations of adverse events from patients.

A lot of the times I find it's hard and I don't think it's an on purpose thing from patients, but I don't necessarily think that we do get every single bit of information all the time.- S11

Different things tend to be reported to different people, depending on the position that the person holds, whether it is a chemo nurse, clinical trials nurse, or physician. It is also human nature to forget things. If it is a very serious event, it is likely to be recorded and made known to others working in the clinical trial setting. However, not all patients understand that these professionals are just as interested in the minute events, such as the minor side effects of a treatment. There is a sense of disconnect in that the patients feel that they are on the

treatment to help their cancer. Many patients decide to put up with side effects in hopes that they can get through the treatment, thinking that it is going to help their cancer, and this often translates to under reporting on the patients' part. Some patients may also perceive that the staff do not want to hear them complaining, they do not want to be seen as 'whiners', so sometimes they will hold things back.

...But the patients of course feel that they're on the treatment to help their cancer [yeah] so there's a little bit of a disconnect there. So they're more interested in what the drug is doing for their cancer and they kind of are hunkered down with the idea, many of them are very stoical right [yeah] they say I'm going to put up with whatever side effects I have to put up with um, to get through this treatment because it's going to help my cancer...- S19

Uncertainty of the Job

Assigning Causality

Assigning causality in early phase oncology clinical trials is a decision making process that is full of uncertainty. It is difficult for these professionals to know there is an explanation for an adverse event, but they rarely feel confident in their causality attribution. Clinicians are asked to make very important decisions when the situations are very vague and the answer is not clear. Answering the unknown is especially prevalent in the early phases of clinical trials. In these stages of a clinical trial, patients are typically in advanced stages of their disease, they have tried numerous other treatments, and some patients have been heavily pretreated. Therefore, a lot of these patients have complicated medical histories, and are more susceptible to other comorbidities and related symptoms that further conflict assigning causality. This makes assigning

causality difficult, and may lead to erroneous causality attributions. This can make it very difficult to determine if the developing agent is having a positive effect on the cancer being treated, which is the primary purpose of the clinical trial.

The majority of clinicians interviewed described a basic chronology of decisions whenever they are dealing with patients in a clinical trial. Clinicians first consider the protocol drug. Typically, little is known about drugs that are new to the clinical setting, and they begin by gathering more information. The information known about these drugs is primarily based on animal testing, which is not entirely applicable to humans. There is not always a dose relationship available to aid in the decision making process. A positive dose response curve suggests that the higher the drug dose, the more severe the adverse event. Cumulative doses are often available, but different dose administrations from cycle to cycle are not.

Supposedly one of the criteria for causality is something like a dose response relationship whereby more of something causes more of an effect. And a patient typically, although we may have that in a cumulative dose, we don't have different doses from cycle to cycle necessarily. So you can't say when you had a little bit of this you felt a little nauseated, now that we're giving you 10 times more you're feeling really nauseated. So we wouldn't have that information typically. - S01

In the lives of these patients, the protocol drug is often used in combination with other drugs, whether it be part of the trial (to help compensate for certain adverse events), part of the patient's treatment regime, or over the counter or complementary therapies the patient is using.

You always look at, I mean there are always so many other confounding variables in this population, especially if their disease is starting to get a bit worse. They go on other medication, right which can impact, you don't know what these newer agents do with any of the other medications that are out there.- S09

When this is the case, it is difficult to distinguish which drug is causing the adverse reaction or if it is a combination of both. In situations where there are more than two drugs, causality could be assigned to a single drug alone, or to a combination of multiple drugs. These drugs can also have disease and food interactions, further complicating the situation. It is also often difficult to distinguish between drug reactions and the progression of a patient's disease. In terms of disease progression, it could be something as simple as a patient becoming increasingly immobile, which could disrupt the role of proper functioning of the rest of the body. Distinguishing between adverse reactions and disease progression can be very difficult, but beyond the uncertainty of the task, it is crucial in determining if the developing agent is indeed working.

Well, I guess as I'm struggling with this in the Phase 1 trials, what's an adverse event. [okay] Because within the protocols they're not defined very well either. So that you could get disease progression that's an adverse event which when you're coming into determining DLT's and moderate toxicity if you put you know, increasing shortness of breath could be related to disease. But when they say it's an adverse event that occurs on study, whether or not deemed related to the investigational agent you can potentially be putting disease progression [right] as an adverse event. Patients may also develop other illness during the duration of the trial, for instance angina or diabetes, further complicating the situation.- S09

Um, yes, I had a patient who ah, developed a pulmonary embolism and we couldn't say for certain it was the chemotherapy she was on. It could have been disease related, it could have been disease progression. There was a number of issues but we weren't clear um, and yeah, we weren't able to assign.- S31

...So I had to think this morning for example this ocular side effect, was it due to you know, drug A or drug B or the combination. Or was it due to something incidental like you know conjunctivitis or something. So you have to think about alternative causes, alternative explanations. I mean people with cancer get many symptoms from the cancer that are not necessarily due to the drug, they may just be due to the underlying disease. And of course a lot of people have comorbidities because they're elderly and have a 101,000 things wrong with them. And you know, is it just something incidental. So I think one of the important things in the causal reasoning is, is to be aware of what the possible causes could be...- S22

Determining causality is difficult because there are often confounding variables. There are a lot of attribution possibilities under the banner of uncertainty. Medical oncologists approach causality assessment in a way that realizes there is an entire slate of factors, which may result, either alone or in combination, to the adverse event under examination.

Again, there's, there are many factors here and um, um, and when you're looking at alternative causes, that's generally where it comes down to an uncertainty.- S30

It was found that clinicians often feel pressured to make the right decision, and that this pressure can even inhibit their ability to make a decision.

Um, because life is full of uncertainty and you know, it's possible to be panicked into, into making a wrong decision. On the other hand it's also possible to be paralyzed into not making any decision at all.- S22

It is evident that, in oncology clinical trials, physicians can feel genuinely uncertain. Uncertainty is indeed at the heart of a majority of causality assessments.

However, it was found that clinicians and physicians alike use a variety of methods to cope with the uncertainty they are faced with in these clinical trial

settings. Firstly, these professionals reassure themselves that causality assessment is never simply black or white; there is often a grey area.

Well because there's a, it may help you sometimes in the dilemma where you in this grey zone of serious adverse event where you think about what to, what to assign to this SAE. If you have a clearly unrelated or clearly related SAE that's easy but the, the vast majority of SAE's is probably somewhere in between..- S14

There always seems to be some element of doubt, and these professionals find comfort in the flexibility that a grey area offers in these difficult situations. There is tangible evidence that there is toxicity, but the reality is that indirect events can subsequently happen. Keeping an open mind, and changing their thinking to incorporate a grey area allows these individuals to feel more confident in their decisions, as opposed to simply saying that it is definitely related or it is definitely not related.

These medical professionals also cope with the uncertainty of these situations by placing a strong emphasis on the timing of an event. According to NDM, this decision making process is seen as a matching process between situations and actions opposed to the generation of any possible option. These experts use “context-bound informal modeling” to make their decisions.²⁵ When making decisions, the professional's knowledge and experience is specific to a natural context (clinical trials), as opposed to a formal decision making model which is context independent.

Given that there are little resources to make these decisions, including inadequate dose relationship knowledge, these professionals place an important emphasis on the timing of an event; the proximal distance between the

administration of a drug and the occurrence of an adverse event. That is to say, the shorter the distance is, the more likely there is a causal relation.

Yeah, and I would say timing is the most important factor. I mean, other factors, we don't usually have dose as a, as a ah, we don't usually have doses in the same, different doses in the same patient to be able to judge a dosing relationship- S01.

It was also found that these medical professionals find it so difficult to make a causality decision when they are with the patient, that they will often, in retrospect, continue to look at the data, even after the patient has left. With time, similar situations may develop with other patients, or may repeat themselves upon dose administration. This gives them a chance to reanalyze the situation, usually with a clearer depiction of what was going on, and make a more accurate decision at a later date.

So sometimes there are grey areas and at the time it might be difficult but retrospectively by continuing to look at data after the fact then you're able to um, to decide at a later date.- S31

Clinicians also cope with uncertainty by erring on the side of caution.

But you have to, I think you have to assume that you don't know enough about the drug that it could be drug related.- S20

Getting to know and understand the patient also plays a role in coping with uncertainty. Patients may have pre-existing conditions, or other health problems that may contribute to some symptoms. There is also the possibility of psychological factors, or changes in the patient environment that may contribute to adverse events.

Say patient fatigue, ah, well that can be really difficult for instance, it could be related to disease, study drug, could be related to psychological factors, some change in the patient's environment, who knows? And that could be, and you have to look at all those and figure out which is most

likely and then it's you know, and have there been changes in those areas that might explain it? Um, and if there's more than a couple of possibilities you have to kind of use your judgment which is more likely.- S20

Sometimes the conflict is a result of the patient's personality; some people may try to downplay their symptoms, and others may exaggerate them. Therefore, understanding the patient can play a key role in coping with uncertainty.

And pre-existing conditions in the patient if they have you know, other health problems that could be contributory to some symptoms. You know, and sometimes it can be as easy as just the person themselves, some people will say they're perfectly fine when they're not. And other patients will elaborate on you know, how they're feeling and might be exaggerating a little bit. So you know you have to try and understand the patient themselves as well.- S27

As difficult as the process of assigning causality is, it was found that professionals use a variety of methods to cope with this uncertainty. Clinicians reassure themselves that the answer is often not black and white, that this grey area exists, and that is acceptable. These professionals also manage uncertainty by placing a strong emphasis on the timing of events, reevaluating decisions at a later time, erring on the side of caution, understanding the patient, and using their experience to make informed decisions.

Subjective Judgments and Experience

Causality assessment in early phase oncology clinical trials is often uncertain because there is rarely objective evidence. These medical professionals agree that most of the time they use their clinical judgment to make a decision. They also all agree that using one's experience to assign causality is a very subjective process.

I have to admit that is very subjective at times.- S13

You know, where the same event can be attributed differently because a lot of things, it's a subjective assessment. It's not as objective as it should be, I think that's what makes it a challenge.- S18

Is it something that has been previously reported or associated with the drug from the investigators brochure or whatever information is available through the trial. And so you just try to gather information around that and then it's a best guess.- S08

Words used to describe clinical judgment included “*common sense*”- S13, “*intuition*”- S22, and “*using your head*”- S03. When utilizing clinical judgment, clinicians gather all the information they can on the adverse event and their patient's status, and from there they will employ a process of elimination.

Inter-Professional Subjectivity

Clinical judgment is really based on experience, and the experience level of each professional varies considerably. Experience can be applied to many aspects of the clinical trial, including experience with a particular patient population, a particular class of agents, or working with a particular drug company.

It's really based on experience at this, at this stage. So really it would depend on a, an experienced investigator who has managed a lot of the specific patient population to in my opinion, accurately determine if this is something that's related.- S06

Given that experience levels vary, there is often inter-professional subjectivity, meaning it is very difficult to come to a unanimous decision. Causality assessment is, in many ways, intuitive and can depend on the physician's interpretations of definitions, as well as their past experiences.

Most of it is kind of intuitive you know, so I'm not sure.- S01

Some professionals may have a lot of experience with a particular class of agents, therefore they may have particular expectations for the developing agent and this may bias the way they attribute causality. Their assessment can also be subjective in terms of the amount of background work a professional does in order to understand an agent. In order to cope with the varying experience levels, some professionals, whom are uncertain about a particular adverse event, will take the extra time to review the investigator brochure or protocol and talk to other investigators about the situation, and others will not.

Well I think it's based on what's been listed in the protocol and possibly the investigator brochure. But really do you have time to look at an investigator brochure every time? No.- S08

It was also reported that when there is more than one professional involved in assigning causality, there is often more than one opinion, and reaching a unanimous decision is a difficult process.

It would have been nice if we could have established causality unanimously but. [yeah] So I say going to the physician but if there is more than one involved there can be more than one opinion. [yes, okay] But generally getting a consensus is helpful if you can go to your physicians and they often are very good at saying well. Even when I don't think it is, they'll say no I think it was you know, the agent that caused this, this is definitely associated and yes we'll say it's, we'll assign causality to that. So I don't try to decide on my own, if I'm not sure I will go and ask [yeah] for other input and then we'll try to make a decision.- S31

Patient Subjectivity

Not only is causality assessment amongst professionals full of subjectivity, but patient experiences are as well. Some adverse events can be objective, for

example weight loss, this is easy to measure in pounds or kilograms. However, how a patient is feeling is very subjective, especially when it comes to pain. Severe pain to someone might be moderate pain to someone else, and mild pain to another individual. Things such as pain, nausea, fatigue, and headaches are very subjective, and that is where it becomes difficult for the physician.

Um, just so there's a general consensus and everybody can talk about it together to really understand what, what the patient is experiencing. Um, and again I think that's very subjective for the clinician also the way the patient describes things.- S11

But when it's subjective, like how a patient is feeling or how sore their mouth is or you know, how much pain they might be experiencing, it's all very subjective to each patient.- S32

Physicians also run into situations where some patients are very detailed and open, they let the clinicians know exactly everything that they have been experiencing with their body, however mild or severe. This could possibly lead to adverse events being over-reported. It is also possible to have patients that do not want to tell the clinician anything, in fear that they are being seen as a bother, or complaining too much. This could possibly lead to under reporting of adverse events. In order to cope with patient subjectivity, physicians will often ask probing questions about side effects, problems, and body systems.

So I think it definitely depends, again, very individual, depends on the patient, depends on your personality, what you're asking. If you're asking the appropriate questions or not, I think that that makes a big, a big difference too.- S11

The primary reason these subjective judgments take place is because there is not a systematic way to make these decisions, so these professionals

are left to base their decisions on hunches and feelings opposed to a rigorous method or measurement tool.

Apprehensive Causality Attributions

With limited resources to aid in assigning causality, these professionals are extremely apprehensive when making attributions. There is this general fear of making the wrong decision, which is primarily based on the very serious consequences of misattributions.

If it's done incorrectly, it's a pain in the ass for all the trial nurses and all the investigators, all the trial doctors all over the world because it takes time to sort out.- S03

There are two 'mistakes' that these professionals fear: a false positive or a false negative causality attribution. Any misestimating can result in risks to the developing agent, or to the patient.

There's, there's two concerns, I think one concern is you know, over assigning causality. Because patients are, they can get sick, morbidities, multiple medications, actually a lot of reasons and it sometimes it's easier to blame it on the drug. But I think my fear is that if you, if you do that liberally you'd be, not discrediting the drug but you're not um, it could lead to dose reductions, could eventually work their way into an ineffective treatment schedule for that. If you saw a whole bunch of side effects that you thought were you know not really related to the drug and that led to that drug being less developed in a certain disease. Maybe you're doing a dis-service to that patient population, so that's one, that's one concern I have. Perhaps over-assigning causality just because of the complications of some of the patients on the program is my biggest concern. And the other concern is, the other, completely opposite really is the not assigning causality and then drugs are allowed to develop. And then it's only when you start getting into Phase 2, Phase 3 studies that you really, adverse events really show themselves. And you're thinking well why wasn't this picked up in the Phase 1 or 2 studies? [yeah] So I think you can go either way, you can make errors on either way, one way you might kill a drug that might be successful and on the other way you might let a drug develop not carefully enough.- S04

I think there's two big concerns. One is if you assign causality and say it's related improperly then it might tarnish a good drug and stop dose escalation in a way that wouldn't be appropriate. Alternatively if you ignore it, it might cause further toxicities in others and be potentially dangerous to other patients. I think it's a very dangerous thing. I also think that sometimes as oncologists we tend to minimize rather than maximize because we're used to toxicity with drugs and that can be dangerous.- S16

Under Attributing Causality

The fear of under attributing causality to the drug being tested stems from the concern for patient safety.

Overlooking it altogether is certainly worse [yeah] but I think [it's also important] a serious adverse event, if a serious adverse event is seen in relationship to this more often then at some point we, we report it. But I think the frequency may then be under reported. But the key, overlooking a side effect or not reporting a serious adverse event which is actually part of the side effect profile, that's probably the worst, the worst thing.- S14

Um, well, of assigning them poorly? It's either you under, or whatever event it was so you're compromising safety of future patients who might go on this treatment if you um, rule that it wasn't related to the drug.- S15

Over looking particular side effects can allow the drug to advance to new phases, when it may not be safe to do so.

So you could in one situation attribute something to an entire one set of the, the most serious and if it's this and you don't acknowledge it, that's dangerous for future patients in the study.- S12

In these situations, serious adverse events may start to arise; these events may have not been reported in earlier phases of the trial, compromising the safety of future patients. In some instances, a potentially dangerous drug may progress so far as to be legalized into the market, harming patients, even leading to fatalities. It is also possible that a very small number of patients in a trial may lead to underestimating or under-relating particular symptoms to the drug. In order to

cope with this 'fear' of under attributing causality, these professionals will often err on the side of caution by attributing adverse events to the drug being tested.

Over Attributing Causality

This is the opposite end of the spectrum, where causality is overly attributed to the protocol drug. There is a lot of pressure placed on these professionals to make the correct decision. However, in situations of uncertainty, these professionals tend to err on the side of caution, out of concern for patient safety, but this may be unfair to the agent under development.

Well, I think you can overcall things that, and say that they're related when they're not. [mmm hmm] Um, and then that leads to for the drug companies to sort out or, or you know, whoever the sponsor is in determining are these or are they not? And I think um, it would be beneficial at some point to follow through on the other end of things to see what it means when you're on that end.- S11

Over attributing causality to the study drug can contaminate the entire database in terms of the causality of these toxicities. The onus on these professionals is extremely high, because they have the ability to undermine the trial by making an erroneous attribution. In these situations, the investigator may be forced to intervene in the conduct of the study, and the administration of the drug. In dose escalation studies, where the dose is increased based on the tolerance to increasing dosages, a drug may not reach the next dose level, or more patients may be recruited to that particular cohort level, subjecting more people to that drug than may be necessary. This may also cause an ineffective dose to be administered to a given cohort of patients, resulting in an ineffective treatment schedule. In some instances, it is possible to delay or even jeopardize the

development of the study drug, which could preclude further study of the drug, or stop the trial all together.

...If you saw a whole bunch of side effects that you thought were you know not really related to the drug and that led to that drug being less developed in a certain disease. Maybe you're doing a dis-service to that patient population, so that's one, that's one concern I have...- S05

...I think one concern is you know, over assigning causality. Because patients are, they can get sick, morbidities, multiple medications, actually a lot of reasons and it sometimes it's easier to blame it on the drug. But I think my fear is that if you, if you do that liberally you'd be, not discrediting the drug but you're not um, it could lead to dose reductions, could eventually work their way into an ineffective treatment schedule for that population...- S04

In these instances, it is unfortunate because the trial may have been well proposed, with a sound hypothesis, yet one could end up rejecting the hypothesis by improperly assigning causality. This also risks the drug not going to market when it may be a potentially legitimate drug. In this case, not only the trial, but the entire enterprise could be undermined, which would compromise many years of work, money, and investment. This could also add additional costs for the company who developed the drug, requiring additional testing, and a significant amount of additional paper work. In order to cope with the 'fear' of over assigning causality, physicians will try to better understand the protocol drug and its sister agents in order to better equip themselves to make these important decisions.

Competing Goals

The apprehensive attitude towards assigning causality can stem from the competing nature of clinical trials. There are often competing goals in the process

of attributing causality, whether it is the workload, timeframe, the patient's well being, or the development of the drug.

Sponsor/Pharmaceutical Company Pressures

Physicians are often apprehensive to assign causality because the trial sponsor has the ability to question their decisions. One of the challenges in oncology clinical trials is balancing patient safety and the development of the protocol drug. These professionals often felt pressured to attribute causality in a certain way to please the sponsor, but were often hesitant because they did not want to risk the patients' safety. Clinicians feel pressured by these companies to limit toxicities. Adverse events attributable to the drug being tested can expand dose levels, placing a financial burden on the company, and extend trial durations.

There's an awful lot of pressure when you're doing early phase studies with a small biotech company. They, there's a lot riding on, on, you know, there are the issues of well are you going to torpedo their only drug or just from a financial point of view, with toxicities that are going to expand the dose level.- S03

These companies can ask clinicians to reconsider their causality attributions and in some instances they will, but more often than not they stick to their original decision.

Um, well they come back and say well are you sure that's related? [mmm hmm] right [yeah] you know. No I'm not sure but I'm not willing to say it's not, you know.- S09

No I haven't because I've stubbornly just said well that's my final answer, so I've never felt any, any sense of coercion. Obviously, you know, inherently results in more work for somebody but ah, in the Phase 1 setting I, I, I think ultimately it's the sponsor's in their best interest to fully understand what their drug is doing and what it's potential effects are. But one does have to be fairly stubborn in that regard.- S06

The company makes their viewpoint well known, and will often try to persuade these physicians to change their decision to better suite the needs of the company.

There's an awful lot of pressure when you're doing early phase studies with a small biotech company. They, there's a lot riding on, on, you know, there are the issues of well are you going to torpedo their only drug or just from a financial point of view, with toxicities that are going to expand the dose level. That's gets in and take longer for the study to complete, those have big financial implications.- S05

Um, well there, you know, there, I think one has to fight, now this is a more of a perception, I don't have any examples. But there's a risk that the sponsor may want, may prefer you to go to an unlikely conclusion. That I disagree with.- S06

Not too much, but then again I'm not the one that the sponsors contacting when they call you and go are you sure that this is what you think it is? and stuff like that. I've had one of those calls where they'll call back and they'll say is this the way you want it? And you just go back to the physician and tell them they want to reconsider. And sometimes the physician is, will stick to their guns and sometimes they will re-think it or whatever.- S07

The cause of these dispositions is sometimes the difference between a primary and a secondary adverse reaction. Most drug companies only want the primary events reported as the serious adverse events; the others are to be covered in the description of the serious adverse events. In some instances, this may in fact be the case; however, where smaller reactions are a result of more serious reactions this may not always be the case.

Sometimes in some places for some companies you know the serious adverse event would be mucositis, diarrhea and dehydration. And other places and I guess the NCIC in particular, I mean our recent experience, is that they say well the drug doesn't cause dehydration, the diarrhea and the mucositis does.- S08

This places physicians in a position where they feel obligated to downplay minor adverse drug reactions to please the drug company. These companies have a tendency to label expected adverse drug reactions as serious adverse events, and unexpected adverse events as less serious. This may not always be the case, but it can influence the way clinicians feel about their attributions.

The company sort of reports basically they, they want to downplay um, these and so their stock standard line is that you know, such and such a side effect is not listed in the investigator brochure, the implication being well it can't be related. So you know they take the, so you've got to look at it with, it's somewhat helpful but somewhat tedious. - S08

With the pressure to keep the drug development process moving, the goal seems to be more directed towards putting patients into a study, than ensuring the safety of a patient in a study. In some instances, where patients experienced an adverse event, interviewees felt they should reduce the dose of the drug being administered or hold off treatment for a certain time frame, however they sometimes felt pressured to continue on with the study. However, in order to cope with the pressures from these pharmaceutical companies, these professionals always keep patient safety at the heart of their attributions.

Drastic Timelines

Other pressures stem from the extreme workload and drastic timelines.

I guess, I guess one of the biggest challenges these days is that if we, people have enough time to rigorously evaluate all the possibilities in a very busy clinic setting. [yeah so] The time to sit down and really fully go over everything with the patient in terms of what's new by history and do a good physical examination.- S20

Who's kidding who, they're busy and overworked, um, and trials are a lot of paper work. So I think that's possible, I certainly don't think there would

be malicious intent [no] but I, but I do think that you know, even time constraints that sort of thing could have, play a factor in that.- S11

In oncology clinical trials, there is a hefty workload in reporting serious adverse events, including a great deal of paper work; it is a very labour intensive process. Interviewees feel a great deal of pressure to attribute causality in a timely manner, which is very difficult to do when they do not have all the information they need to make a secure decision. A serious adverse event needs to be filed within twenty-four hours, placing time constraints on these professionals. These sponsors want an answer right away on what the cause of the adverse event may be. This can be especially difficult in situations where there has only been one individual who has presented this adverse event. Again, these patients typically have multiple comorbidities, and any of these ailments, or a component of them, could be causing this symptom, or it could even just be an abnormal lab result. So there are situations when these professionals will make an assessment that they will subsequently change, or it will become clearer over time, that something else is in fact happening, and they will change their mind. Companies want to know the causality assessment right away so that they can send this information out to other sites. However, the interviewees expressed that they feel pressured to be the ones to make that ultimate decision, when it might not be accurate. In order to cope with this, these professionals rely heavily on their experience to make an educated attribution. These professionals expressed the need for more time to make these decisions, many not understanding what the big rush is all about.

I mean I think um, basically um, if we all had more time in our day it would probably be easier to do it. The SAE has to be filled in within 24 hours. I mean that's another issue, why 24 hours? what's the urgency? By the time we receive it, we send it off to the sponsor, it goes to REB, there's going to be a lag time anyways.- S13

In situations like these, it is imperative to have a dedicated infrastructure to deal with these competing goals. Drug companies want fast attributions and physicians want time to make accurate decisions.

Internal Pressures

There are also financial pressures. Drug companies will often approach a strong academic clinical trials group to sponsor a clinical trial. These companies can often offer more financially than academic investigators, so there is a pressure to accept funding from these companies.

Internal pressures are also present, including competing goals between clinicians and patients. A patient may experience serious toxicities and the clinician will want to stop the drug or reduce the drug dosage; however, the patient can pressure the clinician to keep them on the drug. This can make clinicians feel forced to under-report toxicity, risking the safety of other patients. Clinicians cope with patient pressures by reassuring themselves that patient safety is their top priority.

Yeah, that's a very valid question, sometimes I will have a patient who is having a serious toxicity and I want to stop the drug and the patient is pressuring me to keep on the drug. And you know, if you are going to keep them on the drug then maybe you have to under report the toxicity.- S21

...Um, so, I mean obviously patient safety is paramount...- S26

Clinicians also feel pressure from the Clinical Research Associates (CRAs) assigned to their trial, to attribute things in a certain way. There are situations

where the CRAs have an opinion about what the attribution should be, but it may differ from other investigators' opinions.

Third parties, um, our CRA's sometimes want things attributed in a certain way.- S19

There is pressure to conform to their opinion because, by doing so, it decreases the amount of work for them and cuts down on the amount of time spent on that particular attribution, affording more time to other matters of the trial. However, interviewees cope with these internal pressures by using their best clinical judgment when assigning causality.

Discussion

Table 7 summarizes the main themes found in this study, and shows the interconnectedness between each theme. One of the main themes was the uncertainty of the job, which stems from the lack of objective evidence, causing these professionals to make subjective judgments and relying on their experience to do so. The subjective nature of these causality attributions stems from the lack of resources available to assist these professionals in making informed decisions. This lack of resources also leads to apprehensive behaviour towards attributing causality. Lastly, the apprehensive nature of causality attributions also stems from the competing nature of oncology clinical trials. This table also summarizes the subthemes that were described in the findings sections as grey/problem areas.

The purpose of this study was to come to a psychosocial understanding of how clinicians and oncologists attribute causality in early phase oncology clinical trials. This was achieved through a naturalistic decision making perspective,

which focused on how these professionals actually make decisions in a complex real world environment.^{24,25} Table 8 revisits the themes outlined in the literature review, and indicates the degree that this study supports each theme. These results will be expanded upon in subsequent sections.

Table 6: Discussion of Findings

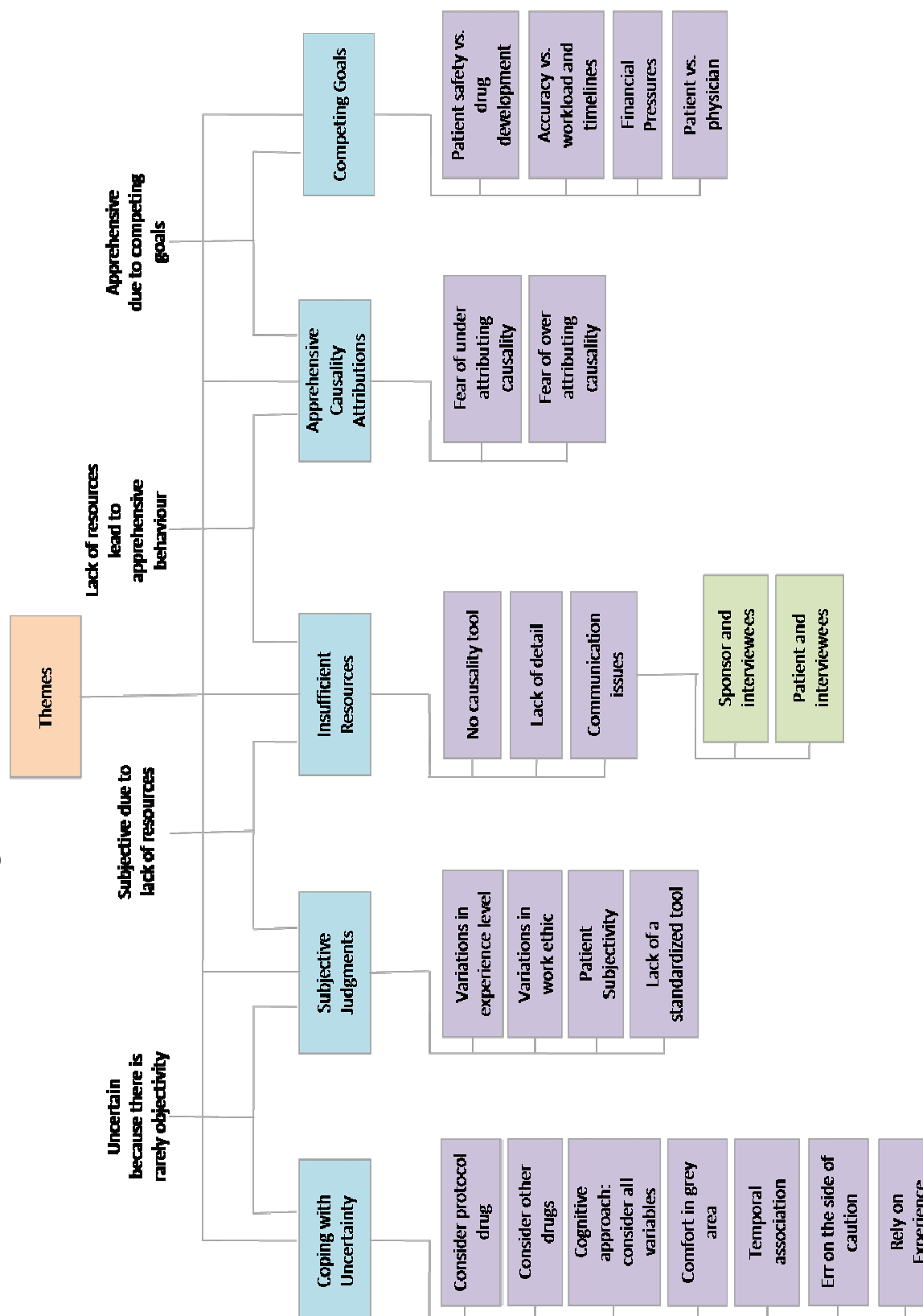


Table 7: Supportive Literature

Themes in Literature Review	Level of Support (Supported, somewhat supported, not supported)
Inconsistent definition of harm	Not supported
Time constraints	Supported
Constraints of error reporting systems	Somewhat supported
Under reporting of adverse events	Supported
Lack of a standardized method for assessing causality	Supported

The literature suggests that there is great variance between a patient's and a physician's interpretation of harm, i.e., a patient experiences an adverse event, and may see it as a harmful reaction, but the physician does not.²⁹ However, this study does not seem to support this finding. There was no inherent discussion of the definition of harm, or how one determines which events are harmful, and which events are not. It was, however, evident that these professionals genuinely expressed concern for their patients' safety. They were more likely to report an adverse event as harmful, based on their clear concern for their patients' safety. It is evident that harm is a very loaded and subjective term, with no standard definition in the clinical trial setting; however, the views of these participants expressed that they are deeply concerned about the safety and well being of their patients, not undermining the harm a patient may feel subject to.

The literature on oncology clinical trials also revealed that time constraints placed added pressure on clinicians.³³⁻³⁵ The findings of this study support this. Time constraints do affect the quality of these decisions as well as the confidence levels of the decision makers. The research aimed to discover how, and to what

extent, time pressures affected these professionals' decision making abilities. It was found that clinicians feel as though they do not have the extra time to reexamine the investigators brochure, search online, or call up other centres if they are uncertain about an attribution. So these professionals are left feeling as though more effort could be put into these decisions, but the time demands on the trial inhibit their ability to do so, and sacrifice the confidence levels of their causality attributions. This study also adds to the literature because participants express that they did not understand the timelines in clinical trials.

Pharmaceutical timelines typically leave these professionals with twenty-four hours to assign causality to an adverse event, but the interviewees did not understand why. There is a lack of communication between trial sponsors and the professionals conducting these trials, further exemplifying the need for change.

Other literature on oncology clinical trials indicates the constraints of error reporting systems. The literature clearly indicates that medical errors are inevitable, and that physicians choose not to report medical errors in fear of being individually blamed.^{38,39} The findings of this study support these results. An exploration of the cognitive underpinnings of causality assessment through NDM revealed that these professionals have a lot of responsibility and can feel the pressures of the job.²⁴ Although there was no direct conversation on reporting medical errors, the findings did show that these professionals largely feared making an error. These professionals were, at times, very apprehensive about attributing causality. A misattribution could have serious consequences for the

development of the drug, or the safety of their patients. Therefore, the results do support the constraints of error reporting systems.

The literature in the field also conveys the severe under reporting of adverse events that take place in oncology clinical trials.^{45,46} Under-reporting can have severe implications on the safety of the patients in these trials..^{48,51} The findings of this study confirm that under attributing causality is still an issue in these trials. A naturalistic decision making perspective allowed for a detailed analysis of causality assessment which revealed that clinicians struggle with under assigning causality for a variety of reasons.^{24,25} Investigators may become largely invested in the study, choosing to minimize adverse events in order to help the drug succeed. There are also situations where investigators may feel pressured by the pharmaceutical companies to under-report, or have their attributions questioned by these companies. A reasonable solution would be to develop a standardized procedure for assigning causality in order to eliminate bias and prevent under reporting of the events, in turn improving patient safety.

Another interesting feature of the interviewees' experiences was their fear of over attributing causality. It was evident in the literature that under reporting serious adverse events was a major issue that had serious consequences; however, there was little mention of over assigning causality.^{45,46} It makes sense that there would be two sides to this dilemma. Over reporting can have serious implications on the development of a drug, the duration of the trial, and can place a financial burden on the company who is sponsoring the trial. These experiences exemplify the constraining nature of these decisions.

The literature also revealed that in oncology clinical trials there is currently no accepted standardized tool for assessing causality, and the current study supported this concept.⁵⁸⁻⁶² It was found that global introspection was indeed the most common method (in this particular study, the only method) used to assign causality. Global introspection does not use a tool, but instead uses prior knowledge and experience to make an educated decision.⁵⁹ However, as mentioned in the literature review, and supported by the current study, this process is full of subjectivity, and therefore, has low reproducibility standards and questionable.⁵⁹ In addition, this study found that these participants had a high interest in the development of a standardized tool. They were open to the idea of accepting and adapting a standardized tool. All experts agreed that a tool like this would be helpful, and would aid them in making more confident decisions.

These professionals shared how assigning causality was an extremely subjective experience, which always seemed to be interpreted as a bad thing in this medical setting. There seems to be an inherent battle between subjectivity and objectivity in oncology clinical trials.⁸²⁻⁸⁴ If attributing causality is seen as subjective, it needs to be more objective, and if the decision is objective, it needs to be more subjective. Where is the balance between the two? According to the current study, being subjective in one's judgments is not inherently a bad thing. In fact, none of the participants could identify a tool they used to attribute causality. In all instances, they used some form of global introspection to make their decision(s). However, due to its subjectivity, global introspection is criticized

on aspects of reproducibility.^{59,60,85,86} However, without a standardized tool, all causality attributions can be seen as falling short of reproducibility standards.

Yes, clinical judgments are based on the experiences of these professionals, but is that not a good thing? Experience is a subjective feature, but this is one of ways these professionals cope with the uncertainty of the job. In fact, clinical judgment, or relying on one's experience, was the primary strategy for coping with grey areas within the clinical trial. Even existing causality assessment tools such as, the Bayesian Approach or algorithms, can be criticized based on aspects of objectivity. These methods seem to distance the patient from the decision making process by limiting their involvement and are criticized for lacking clinical

judgment.^{59,60,62} It is clear that oncology clinical trials need to find a balance between subjectivity and objectivity.

Another surprising finding was the lack of education and training received by these professionals to assign causality. In almost all instances, the interviewees could not recall being trained, especially in a formal manner. Most of these professionals

What is already known on this topic

Causality attribution is uncertain in nature

There is no universally accepted tool for assigning causality

Severe under reporting of adverse events

There are often external pressures from pharmaceutical companies and sponsors placed on these professionals

What this study adds

Professionals use a variety of techniques to cope with the uncertainty of the task

The willingness of these professionals to accept and adapt a standardized tool

This general fear of misattributing including over reporting adverse events

There are also internal pressures placed on these professionals; in particular patient pressures

engaged in on-the-job training, which was, for the most part, self taught. This could be a reason for the high volume of professionals relying on clinical judgments or global introspection to make these decisions. If they had indeed received a formal training session on how to utilize a particular algorithm or Bayesian approach, their experiences may have been vastly different. Although clinical judgment is a well respected and commonly used tool amongst these professionals, training could be used to promote consistency and provide further validity to the approach.

There are no standard definitions of scale measures when assigning causality. This can greatly contribute to inconsistency amongst professionals and discrepancies between pharmaceutical companies and trial investigators. Clinicians are given a variety of scale measures to attribute causality. These mainly consist of terms such as 'certain', 'probable', 'possible', and 'unlikely'. However, these terms are rather vague for such an important decision, especially when they lack standard definitions. Perhaps if formal training in regards to causality assessment was a common practice in oncology clinical trials, there would be less concern with attribution scale measures. It is proposed that standard terminology be developed for these scale measures. Even if a hypothetical situation indicating percentiles for particular attributions was developed, it would promote greater consistency amongst these attributions and allow clinicians to feel more confident in their decision making abilities.

After a thorough explication of the data, it is evident that a standard, more inclusive definition of ADRs needs to be established. The definition needs to

account for minor reactions and error, as well as deemphasize the harmfulness of these events. A more inclusive definition of a serious ADR would be a response to a drug or medical intervention that significantly affects quality of life at doses intended for prevention, diagnosis and treatment of disease, which warrants changes in dose administration, including withdrawal of the product, and prophesizes risk from future administration. This definition is based on scientific research and is derived from the data explication process. This offers a more holistic approach to defining ADRs.

With reference to Figure 1- The Steps in Assigning Causality, the findings are in full support of the concepts presented in this diagram. The interviewees clearly indicated the steps that they take when attributing causality and outlined the role patients play in this process. While Figure 1 is a clear representation of the steps involved in assigning causality, the revised diagram (Figure 3) below presents the main themes of this study's findings.

Figure 3: The Steps in Assigning Causality Revised

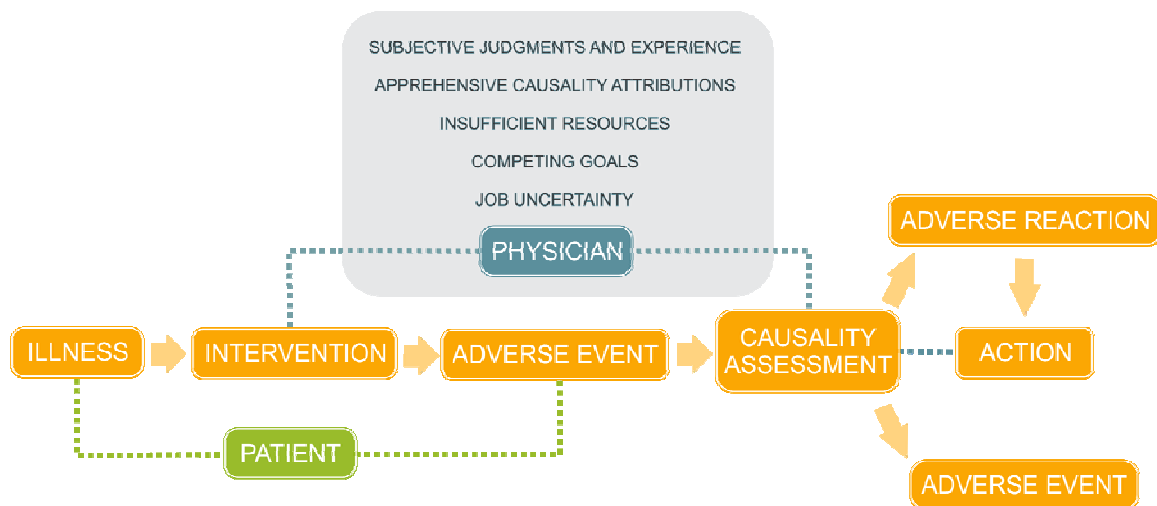


Figure 1

A naturalistic decision making perspective proved to be an effected guide for data explication.^{24,25} It is evident that the participants are experienced professionals who are making important decisions that are constrained by time, uncertainty, and competing goals. These professionals use a variety of methods to cope with difficult decisions, but primarily drew on their experience to make sense of situations in order to make proficient decisions. NDM is an excellent decision making theory that is flexible and leaves room for individual variation, as well as allowing for the conclusion of complex and dynamic environments.

Comparison to the Original Research Study

The original research sought to understand clinical reasoning, the tools used to assign causality as well as the challenges present in this process. The current differed in that it examined these issues through the lens of a theoretical framework- Naturalisitic Decision Making. NDM added a unique psychosocial

perspective on these various elements of oncology clinical trials serving as a solid foundation for this research study.

The purpose of the original study was to explore the perceptions and opinions of the participants. Being phenomenological in nature, the current studied purpose was to explore the lived experiences of the phenomenon of assigning causality. The original study conducted both a content and thematic analysis, and the current study increases the trustworthiness of these findings through analyst triangulation. Lastly, the findings of the original research study described the steps in assigning causality. The current study described the problem or grey areas that arise when assigning causality, explored the implications of those problem areas, and identified coping strategies for dealing with these issues.

Table 8: Variances From Original Research

Original Research Study	Current Study
<ul style="list-style-type: none"> • Clinical reasoning • Tools used • Challenges faced 	<ul style="list-style-type: none"> • Studies these things through the theoretical framework of Naturalistic Decision Making (NDM) – Psychosocial perspective
<ul style="list-style-type: none"> • Explored perceptions and opinions 	<ul style="list-style-type: none"> • Explored the lived experience (phenomenon of assigning causality)
<ul style="list-style-type: none"> • Content & thematic analysis 	<ul style="list-style-type: none"> • Added validity through analyst triangulation
<ul style="list-style-type: none"> • Described steps in assigning causality 	<ul style="list-style-type: none"> • Described grey/problem areas, implications, and coping strategies of those steps

Limitations and Delimitations

Limitations

One of the main limitations to this study was that it was based on secondary data analysis. The researcher did not conduct the interviews, nor transcribe them. This put the researcher at a small disadvantage when it came to analyzing the data. Due to the fact that the researcher was not present during the interview and has no audio-representation of the data, the researcher solely relied on the transcribed data. This distance from the original content did pose a challenge to the researcher in terms of gathering the overall essence of the interviews. However, the researcher was still close enough to the data to minimize any decrease in sensitivity toward to phenomenon.⁸⁷ Secondary data analysis also posed many advantages to this research study.^{88,89} More time was devoted to the data analysis stage of this research.⁷⁴ Access and rapport are also major advantages of this secondary data analysis. The group of professionals who collected the data had access to major cancer research centres throughout Canada, as well as funding from AstraZeneca, Canada Inc. The data were collected with proficiency and professionalism, which would otherwise not be accessible to this thesis. Another advantage was that the questions presented in the interview guide were relevant to research questions proposed in this study. Secondary data analysis contributes to the likelihood that the data is used to its full potential.⁸⁷

Other limitations included that recruitment was restricted to professionals in academic cancer centers across Canada. The findings of this study may differ in other countries.

Delimitations

This research aimed to come to a psychosocial understanding of causality assessment in early phase oncology clinical trials. This research, however, did not create a tool to be used to assign causality. Given the time frame required to complete a Master's degree and the breadth of interview data available, there was not a sufficient amount of time to accomplish this. This does however, pose an excellent opportunity for a Doctoral thesis. With more time, a tool could be created, implemented, and revised with the aid of NDM, which would aid oncologists and clinicians in making important decisions within oncology clinical trials.

Strengths/ Contributions

As with many professionals, clinicians and oncologists are faced with many difficult decisions on a daily basis. They must determine whether an adverse reaction is due to the drug/intervention being tested, or do to external sources, unrelated to the trial. In doing so, they are faced with time pressures and bouts of uncertain information, which make it difficult for these professionals to feel confident and secure with their causality assessment. By coming to a psychosocial understanding of causality assessment in early phase oncology clinical trials, a better understanding of how these decisions are being made, what affects these decisions, and the challenges faced by the professionals

making these decisions, was established. Through analyzing these interviews, with the aid of the NDM, the present study has elicited findings that will improve the causality assessment of oncology clinical trials.^{24,25} This is critical because assigning causality plays a major role in patient safety, as well as the market life of a drug. These findings may expand beyond oncology clinical trials alone, into other areas of health research. The findings of this study may also be useful for pharmaceutical companies in terms of provided more detail in IBs, creating more clear expectations for causality assessment and narrowing the communication gap between their company and the professionals conducting these trials at various sites.

It was evident in the literature that causality attributions in oncology clinical trials are uncertain in nature. However, this study adds a new perspective by identifying a variety of methods used by these professionals to cope with the uncertainty of the job. It was also evident in the literature that under-reporting is a serious issue with strong implications for patient safety. However, this study also found that an apprehensive attitude towards over assigning causality was common among professionals. These professionals did not want to jeopardize the agent under development. The literature clearly indicates that there is currently no universally accepted tool for assigning causality. However, what this study adds is the willingness of these professionals to accept and adapt a standardized tool. Lastly the literature outlines that there are external pressures present in oncology clinical trials, but makes little mention of internal pressures

coming from clinical research associates and patients in the trial, which this study found to be a common experience.

The results of this study will also contribute to the ongoing development and refinement of the NDM theory.^{24,25} The current research on NDM deals with professionals, such as firefighters, pilots, business executives, soldiers, technicians, and physicians.⁹⁰ However, previous information on physician decision making using NDM dealt primarily with emergency situations i.e., paramedics and emergency room staff, which vary greatly from the setting(s) presented in oncology clinical trials. To date, no research has been found that examines clinicians' and oncologists' decision-making through a NDM framework. Therefore, the present study provides a noteworthy contribution to the literature surrounding NDM.

Ideas for Future Research

It is very difficult to keep consistency between professionals when there is no universally accepted tool to assign causality. Subsequent research includes using the information gathered from this study could be used to design and evaluate a standardized tool that can be used for causality assessment in early phase oncology clinical trials. With a deep understanding of the decision making process, the goal of designing a standardized tool is closer to reality. Such a tool will aid clinicians in dealing with time constraints without sacrificing the quality of their decision-making.

Subsequent research can also involve developing standardized definitions of causality scale measures. Scale measures typically consist of terms such as

'certain', 'probable', 'possible' and 'unlikely'. However, without standardized definitions, these scale measure can greatly contribute to inconsistent causality attributions amongst professionals. Standard definitions would promote consistency between professionals and between investigators and trial sponsors.

Other subsequent research involves developing a training program for causality assessment in early phase oncology clinical trials. It is hypothesized that the reason for the high utilization of clinical judgment stems from the lack of formal training. Clinical judgment is criticized on aspects of validity primarily because of its low reproducibility rates. If formalized training were introduced, it is hypothesized that this would promote greater consistency when using clinical judgment, and therefore raise reproducibility rates. However, if a standardized tool were developed, this, along with causality scale measures could become a standard practice for training. This future research could help eliminate error, improve patient safety, narrow communication gaps, promote more confident attributions, and promote consistency amongst professionals.

References

1. Friedman LM, Furberg CD, Demets DL: Fundamentals of Clinical Trials. New York, NY, Springer-Verlag, 1998
2. Todd MM: Clinical research manuscripts in anesthesiology. J Am Soc Anesthesiol 95:1051-1053, 2001
3. Steinbrook R: Public registration of clinical trials. N Engl J Med 351:315-317, 2004
4. Dewys WD, Malone WF, Butrum RR, et al: Clinical trials in cancer prevention. Cancer 58:1954-1962, 1986
5. Stewart D, Kerr DJ: Clinical Trials Explained, in Kerr DJ, Knox K, Robertson DC, et al (eds): Clinical Trials Explained: A Guide to Clinical Trials in the NHS for Healthcare Professionals. Malden, MA, Blackwell Publishing Ltd, 2006, pp 4-18
6. Kulakowski EC, Chronister LU: Research Administration and Management. Mississauga ON, Jones and Barrlett Publishers, 2006
7. Kelly WK, Halabi S: Oncology Clinical Trials. New York, NY, Demos Medical Publishing, 2009
8. Everitt B, Pickles A: Revised Edition: Statistical Aspects of the Design and Analysis of Clinical Trials. London, UK, Imperial College Press, 2004
9. Society CC: http://www.cancer.ca/Canada-wide/Cancer%20research/Clinical%20trials.aspx?sc_lang=en, Canadian Cancer Society, 2010
10. Gambrill S, Zisson S: The Emerging Markets of Clinical Research. Boston, MA, CnterWatch a division of Jabson Medical Information, 2007
11. Craig A: Clinical laboratory safety data in drug studies, in Talbot J, Waller P (eds): Stephen's Detection of Adverse Drug Reactions. Toronto, ON, Wiley & Sons, 2005, pp 243-290
12. Farcus A, Bojita M: Adverse drug reactions in clinical practice: A causality assessment of a case of drug-induced pancreatitis. J Gastrointestin Liver Dis 18:353-358, 2009
13. Jones O: Managing a suspected adverse drug reaction. Student Br Med J 9:261-304, 2001
14. Richards V: The Wayward Cell: It's Origins, Nature, and Treatment. Berkeley, LA, University of California Press, Lts, 1972
15. Edwards IR, Aronsom JK: Adverse drug reactions: Definitions, diagnosis and management. Lancet 356:1255-1259, 2000
16. Kahn SA: Descriptions of adverse drug events should be standardized. Br Med J 319:127, 1999
17. Canadian adverse drug reaction monitoring program guidelines for voluntary reporting of adverse drug reactions by health professionals, in Programme TP (ed):
18. Ocloo JE: Harmed patients gaining voice: Challenging dominant perspectives in the construction of medical harm & patient safety reforms. Soc Sci Med, 2010

19. Frankenfeld C: "Serious" and "severe" adverse drug reactions need defining. *BMJ* 329:573, 2004
20. Mukherjee SD, Coombes ME, Levine M, et al: A qualitative study evaluating the attribution for serious adverse events during early phase oncology clinical trials. *Invest New Drugs*
21. Boulton M, Fitzpatrick R, Swinburn C: Qualitative research in health care: II. A structured review and evaluation of studies. *J Eval Clin Pract* 2:171-179, 1996
22. Laksham M, Sinha L, Biswas M, et al: Quantitative vs. qualitative research methods. *Indian J Pediatr* 67:369-377, 2000
23. Vincent AA, Norma TM: Theoretical frameworks in qualitative research. Thousand Oaks, CA, Sage, 2006
24. Rosen MA, Salas E, Lyons R, et al: Expertise and naturalistic decision making in organizations: Mechanisms of effective decision making, in Hodgkinson GP, Starbuck WH (eds): *The Oxford Handbook of Organizational Decision Making*. New York, NY, Oxford University Press, 2008
25. Goldoff AC: Naturalistic decision making. *Encyclopedia of Public Administration & Public Policy*, Second Edition, 2008
26. Flin R S, K, Slaven G: Emergency Decision Making the Offshore Oil and Gas Industry. *Human Factors* 38:262-277, 1996
27. Flazer PR: Cognitive scheme and naturalistic decision making in evidence-based practices. *JMI* 37:86-89, 2004
28. Cook DJ, Mulrow CD, Haynes RB: Systematic reviews: Synthesis of best evidence for clinical decisions. *Ann Intern Med* 126:376-380, 1997
29. Meslin EM: Protecting human subjects from harm through improved risk judgements. *IRB: Ethics and Humane Research* 12:7-10, 1990
30. Basch E, Jia X, Heller G, et al: Adverse symptom event reporting by patient vs. clinicians: Relationships with clinical outcomes. *J Natl Cancer Inst* 101:1602-1603, 2009
31. Koch-Weser J, Sellers EM, Zacest T: The ambiguity of adverse drug reactions. *Europ J Clin Pharmacol* 11:75-78, 1977
32. Airmone Y, Bégaud B, Miremont-Salamé G, et al: Agreement of expert judgment in causality assessment of adverse drug reactions. *Eur J Clin Pharmacol* 61:169-173, 2005
33. Betancourt BY, Marrero-Miragya MA, Jiménez-López G: Pharmacovigilance program to monitor adverse reactions of recombinant streptokinase in acute myocardial infarction. *BMC Clin Pharmacol* 5:1-7, 2005
34. Ioannidis JPA, Lau J: Completeness of safety reporting in randomized trials: An evaluation of 7 medical areas. *JAMA* 285:437-439, 2001
35. Vallano A, Cereza G, Pedròs C, et al: Obstacles and solutions for spontaneous reporting of adverse drug reactions in the hospital. *Br J Clin Pharmacol* 60:653-658, 2005
36. Karvinen KH, DuBose KD, Carney B, et al: Promotion of physical activity among oncologists in the United States. *J Support Oncol* 20:835-841, 2010

37. Cosby J: A summary review of 'to err is human: Building a safer health system' and 'Crossing the quality chasm: A new health system for the 21st century'. Hamilton, ON, Program Evaluation & Policy Research Consulting Ltd., 2005
38. Elder N, Palleria H, Regan S: What do family physicians consider an error? A comparison of definitions and physician perception. *BMC Fam Pract* 7:73, 2006
39. Kuzel A, Woolf S, Gilchrist V, et al: Patients reports of preventable problems and harms in primary care. *Ann Fam Med* 2:333-340, 2004
40. Doing what counts for patient safety: Federal actions to reduce medical errors and their impact. Report of the Quality Interagency Coordination Task Force (Qulc) To the President, 2000
41. Rickles NM, Wertheimer AI, Smith MC: Social & Behavioural aspects of pharmaceutical care, second edition. Sudbury, MA, Jones and Barlett Publishers, 2010
42. Westwood M, Rodgers M, Sowden A: Patient safety: Mapping the literature. Birmingham, PSRP, 2002
43. Campbell CT, Campbell TM: The China Study. Dallas, TX, Benbella Books, Inc., 2006
44. Watcher RM, McDonald KM, Duncan B: Making health care safer: A critical analysis of patient safety practices, 2001
45. Bate A: The use of a Bayesian confidence propagation neural network in pharamcoviligance. Umeå, Sweden, Division on Clinical Pharmacology, Department of Pharmacology and Clinical Neuroscience, Umeå University, 2003
46. Hickman M, Aldous J, Gazzard B, et al: AIDS surveillance: A direct assessment of under-reporting. *AIDS* 7, 1993
47. Fromme EK, Eilers KM, Mori M, et al: How accurate is clinician reporting of chemotherapy adverse effects? A comparison with patient-reported symptoms from the quality of life questionnaire C30. *J Clin Oncol* 22:3485-3490, 2004
48. Alsheikh-Ali AA, Karas RH: Ezetimibe, and the combination of ezetimibe/simvastin, and risk of cancer: A post-marketing analysis. *J Clin Lipidol* 3:138-142, 2009
49. Bégaud B, Martin K, Haramburu F, et al: Rates of spontaneous reporting of adverse drug reactions in France. *JAMA* 288:1585-1588, 2002
50. Mahoney MR, Sargent DJ: Adverse-event rates: Journals versus databases. *Lancet* 369:127-130, 2007
51. McClure DL: Improving drug safety: Active surveillance systems should be a paramount. *Pharmaceut Med* 23:127-130, 2009
52. Karch AM: Lippincott's guide to preventing medication errors. Ambler, PA, Lippincott Willimans & Wilkins, 2003
53. McCarthy M: US cancer group calls for a centralized review of clinical trials. *Lancet* 361:1621, 2003
54. Woody GE, Senay EC, Geller A, et al: An independent assessment of MEDWatch reporting from abuse/dependence withdrawal from Ultram. *Drug Alcohol Depend* 7, 2003

55. Scharf O, Colevas AD: Adverse event reporting in publications compared with sponsor database for cancer clinical trials. *J Clin Oncol* 24:3933-3938, 2006
56. Kelly WN, Arellano FM, Barnes J, et al: Guidelines for submitting adverse event reports for publication. *Pharmacoepidemiol Drug Saf* 12:581-587, 2007
57. Pillans PI: Clinical perspectives in drug safety and adverse drug reactions: Drug regulation & drug safety. *Clin Pharmacol* 1:695-705, 2008
58. Ioannidis JPA, Lau J: Improving safety reporting from randomized trials. *Drug Saf* 26:77-84, 2002
59. Agbabiaka TB, Savovic J, Ernst E: Methods for causality assessment of adverse drug reactions: A systematic review. *Drug Saf* 31:21-37, 2008
60. Coombes M, Mukherjee S, Kowaleski B, et al: A tool for assessing adverse events in phase I/II oncology clinical trials. *J Clin Oncol* 25:6518, 2007
61. Molokhia M, Tanna S, Bell D: Improving reporting of adverse drug reactions: A systematic review. *J Clin Epidemiol* 1:75-92, 2009
62. Shakir SAW: Causality and correlation on pharmacovigilance, in Talbot J, Waller P (eds): *Stephen's Detection of Adverse Drug Reactions*. Toronto, ON, Wiley & Sons, 2010, pp 329-343
63. Trotti A, Bentzen SM: The need for adverse effects reporting standards in oncology clinical trials. *J of Clin Oncol* 22:19-22, 2004
64. Creswell JW: *Qualitative inquiry & research design: Choosing among five approaches*. Thousand Oaks, CA, Sage Publications, Inc., 2007
65. Lather P: Paradigm proliferation as a good thing to think with: Teaching research in education as a wild profusion. *Int'l J Qualitat Stud Ed* 19:35-57, 2006
66. Maycut P, Morehouse R: *Beginning qualitative research: A philosophic and practical guide*. Bristol, PA, The Falmer Press, 1994
67. Willis J: *Foundations of qualitative research: Interpretive and critical approaches*. Thousand Oaks, CA, Sage Publications, Inc, 2007
68. Groenewald T: A phenomenological research design illustrated. *Int'l J Qualitat Meth* 3, 2004
69. Osborne J: Some similarities and differences among phenomenology and other methods of psychological qualitative research. *Can Psychol* 35:167-185, 1994
70. Parker L: Qualitative research, in Burton S, Steane P (eds): *Surviving Your Thesis*. New York, NY, Routledge, 2004, pp 159-177
71. Sciarra D: The role of the qualitative researcher, in Kopala M, Suzuki L (eds): *Using qualitative methods in psychology*. Thousand Oaks, CA, Sage, 1999, pp 37-48
72. Kvale S, Brinkman S: *Learning the craft of qualitative research interviewing*. Thousand Oaks, CA, Sage, 2009
73. Hycner R: Some guidelines for the phenomenological analysis of interview data. *Hum Stud* 8:179-303, 1985
74. Boslaugh S: *Secondary data sources for public health: A practical guide*. New York, NY, Cambridge University Press, 2007

75. Moustakas C: Phenomenological Research Methods. Thousand Oaks, CA, Sage, 1994
76. Sadala MLA, Adorno RdF: Phenomenology as a method to investigate the experiences lived: A perspective from Husserl and Merleau Ponty's thought. *Journal of Advanced Nursing* 37:289-293, 2001
77. Hycner RH: Some guidelines for the phenomenological analysis of interview data, in A B, G BR (eds): *Qualitative research* London, Sage, 1999, pp 143-164
78. Holloway I: *Basic concepts for qualitative research*. Oxford, Blackwell Science, 1997
79. Benzin NK: *Sociological Methods*. New York, McGraw Hill, 1978
80. Patton MQ: Enhancing the quality and credibility of qualitative analysis. *HRS: Health Services Research* 34:Part II: 1189-1208, 1999
81. Devers KJ: How will we know "good" qualitative research when we see it? Beginning the dialogue in health services research. *Health Serv Res* 34:1153-1188, 1999
82. Alexander HA: Physiotherapy Student Clinical Education: the influence of subjective judgements on observational assessment. *Assessment & Evaluation in Higher Education* 21:357-366, 1996
83. Leder D: Clinical interpretation: The hermeneutics of medicine. *THEORETICAL MEDICINE AND BIOETHICS* 11:9-24, 1990
84. Wulff H: The two cultures of medicine: objective facts versus subjectivity and values. *J R Soc Med* 92:549-552, 1999
85. Lane DA: Subjective probability and causality assessment. *Applied Stochastic Models and Data Analysis* 5:53-76, 1989
86. Macedo AF, Marques, F. B., Ribeiro, C. F., Teixeira, F.: Causality assessment of adverse drug reactions: comparison of the results obtained from published decisional algorithms and from the evaluations of an expert panel, according to different levels of imputability. *J Clin Pharm Ther* 28:137-143, 2003
87. Hinds PS, Vogel, R. J., Clarke-Steffen, L.: Qualitative Data Set The Possibilities and Pitfalls of Doing a Secondary Analysis of a Qualitative Health Research 7:408-424, 1997
88. Herron DG: Secondary data analysis: research method for the CNS. *Clinical Nurse Specialist* 3:66-69, 1989
89. Corti LB, L.: Strategies in Teaching Secondary Analysis of Qualitative Data. *Qualitative Social Research* 6, 2005
90. Zsombok CE: Naturalistic decision making: Where are we now?, in Zsombok CE, Klein GA (eds): *Naturalistic Decision Making*. Mahwah, NJ, Lawrence Erlbaum Associates, Inc., 1997

Appendix 1: Review of the Literature Search Parameters

Journal/Database	Search Parameters	Number of Results	Elimination/Selection Criteria	Chosen Articles
Academic Search Premier	“expert judgment” + “causality assessment”	1	Fit search parameters	Airmone Y, Bégaud B, Miremont-Salamé G, et al: Agreement of expert judgment in causality assessment of adverse drug reactions. Eur J Clin Pharmacol, 61:169-173, 2005
Academic Search Premier	“review of clinical trials” + “cancer” in TI Title	6	Must contain key term “adverse event”, studies various types of cancers	McCarthy M” US cancer group calls for a centralized review of clinical trials. Lancet, 361:1621, 2003
Academic Search Premier	“safety reporting” + “clinical trials”	11	Only articles involving cancer subjects	Ioannidis JPA, Lau J: Improving safety reporting from randomized trials. Drug Safety, 25, 77-84, 2002
Google Scholar	allintitle: “cancer” + “post-marketing analysis”	1	Fit search parameters	Alsheikh-Ali AA, Karas RH: Ezetimibe, and the combination of ezetimibe/simvastatin, and risk of cancer: A post-marketing analysis. J Clin Lipidol, 3:138-142, 2009
Google Scholar	allintitle: “clinician reporting” + “adverse effects”	1	Fit search parameters	Fromme EK, Eilers KM, Mori M, et al: How accurate is clinician reporting of chemotherapy adverse effects? A comparison with patient-reported symptoms from the quality of life questionnaire C30. J Clin Oncol,

Journal/Database	Search Parameters	Number of Results	Elimination/Selection Criteria	Chosen Articles
Google Scholar	allintitle: "improving reporting of adverse drug reactions"	3	Included review articles.	22:3485-3490, 2004 Molokhia M, Tanna S, Bell D: Improving reporting of adverse drug reactions: A systematic review. J Clin Epidemiol, 1:75-92, 2009
Google Scholar	allintitle: "safety reporting" + "randomized trials"	4	Eliminated studies on mental health and antidepressants	Ioannidis JPA, Lau J: Completeness of safety reporting in randomized trials: An evaluation of 7 medical areas. JAMA, 285: 437-439, 2001 Ioannidis JPA, Lau J: Improving safety reporting from randomized trials. Drug Saf, 26:77-84, 2002
Google Scholar	allintitle: "spontaneous reporting" + "adverse drug reactions" + "rates"	2	Fit search parameters	Bégaud B, Martin K, Haramburu F, et al: Rates of spontaneous reporting of adverse drug reactions in France. JAMA, 288:1585-1588, 2002
Google Scholar	"completeness of safety reporting on randomized trials: An evaluation of 7 medical areas"	195	Title match	Ioannidis JPA, Lau J: Completeness of safety reporting in randomized trials: An evaluation of 7 medical areas. JAMA, 285: 437-439, 2001
Google Scholar	"methods for causality"	34	Eliminated studies looking at one	Agbabiaka TB, Savovic J, Ernst E: Methods for causality assessment of

Journal/Database	Search Parameters	Number of Results	Elimination/Selection Criteria	Chosen Articles
	assessment" + "adverse drug reactions" + "clinical trials"		specific case report, looked to a more general analysis of causality tools. Selected articles whose main purpose was to review current methods of causality assessment. Because methods are continuously evolving, only articles post 2007 were included.	adverse drug reactions: A systematic review. Drug Saf, 31: 21-37, 2008
Google Scholar	"patient vs clinician" + "adverse event reporting"	1	Fit search parameters	Basch E, Jia X, Heller G, et al: Adverse symptom event reporting by patient vs clinicians: Relationships with clinical outcomes. J Matl Cancer Inst, 101:1602-1603, 2009
Google Scholar	"tool for assessing adverse events" + "oncology clinical trials"	1	Fit search parameters	Coombes M, Mukherjee S, Kowaleski B, et al: A tool for assessing adverse events in phase I/II oncology clinical trials. J Clin Oncol, 25:6518, 2007
Journal of Clinical Oncology	"adverse event reporting" + "publications" +	4613	Only selected articles that contained the	Scharf O, Colevas AD: Adverse event reporting in publications compared with sponsor database for cancer clinical

Journal/Database	Search Parameters	Number of Results	Elimination/Selection Criteria	Chosen Articles
	"database"		search parameters in the title, sorted by prevalence	trials. J Clin Oncol, 24: 3933-3938, 2006
MEDLINE via PubMed	"adverse effects reporting standards" + "oncology clinical trials"	2	Eliminated the article based solely on phase 1 oncology clinical trials and toxicity reporting	Trotti A, Bentzen SM: The need for adverse effects reporting standards in oncology clinical trials. J of Clin Oncol, 22:19-22, 2004
MEDLINE via PubMed	"Edwards" + "Aronson"	9	Only those articles related to adverse drug reactions were selected	Edwards IR, Aronson JK: Adverse drug reactions: Definitions, diagnosis and management. Lancet, 356:1255-1259, 2000
MEDLINE via PubMed	"submitting adverse event reports" + "publication"	3	All the same article	Kelly WN, Arellano FM, Barnes J, et al: Guideline for submitting adverse event reports for publication. Pharmacoepidemiol Drug Saf, 12:581-587, 2007
Pub Med	"journals versus databases" + "adverse event"	2	Eliminated those, which were drug specific.	Mahoney MR, Argent DJ: Adverse-event rates: Journals versus databases. Lancet, 369: 1621, 2003
Web of Science	Title="ambiguity" + "adverse drug reactions"	2	Only those articles related to oncology were selected	Koch-Weser J, Sellers EM, Zacest R: The ambiguity of adverse drug reactions. Europ J Clin Pharmacol, 11:75-78, 1977
Web of Science	Title = "preferences" + "decision making" + "patients with"	2	Only those articles related to patients undergoing treatment, including clinical trials were	Hubbard G, Kidd L, Donaghy E: Preferences for involvement in treatment decision making of patients with cancer: A review of the literature. Europ J of Oncol Nurs, 12:299-318, 2008

Journal/Database	Search Parameters	Number of Results	Elimination/Selection Criteria	Chosen Articles
	cancer"		selected	

Appendix 2: Interview Guide

Semi-structured questions:

- 1) Clinical Reasoning:
 - i) Explanation of how a report of a serious adverse event is handled/processed
 - ii) Factors considered when assessing causality?
 - iii) General guidelines followed when assigning causality?
- 2) Information Resources (e.g. Investigator's Brochure):*
 - i) Resources referred to when assigning causality?
- 3) Tools (e.g. decision trees):
 - i) Awareness of tools to help assign causality?
 - ii) Tools used to help assign causality?
- 4) Challenges / Concerns:
 - i) Problems or challenges with assigning causality?
 - ii) Concerns about how clinical trial researchers currently assign causality?
 - iii) External influences/pressures from third parties when assigning causality?
 - iv) What would make assigning causality easier?
- 5) Education:.*
 - i) Formal and informal training received with respect to assigning causality?
 - ii) Educational needs around causality assessment?

* Although the domains of Information Resources and Education were explored in the interviews the findings are beyond the scope of what is presented here.

Appendix 3: Letter of Invitation



May 3, 2006

Dear:

We are developing a tool to assist clinicians in assigning causality to adverse events (AEs) that occur during early oncology clinical trials. In order to ensure that this tool is useful to clinicians, we are conducting a research project that will identify the current decision-making processes used by clinicians and the criteria that are essential for an AE causality assessment tool.

We would like to invite you to participate in our research through a brief in-person interview of approximately 30 minutes in length. The interview would focus on the clinical reasoning you use when assigning causality to AEs and the criteria you feel are essential for a causality assessment tool. Your skills, knowledge, and expertise in early oncology clinical trials would provide an excellent basis for our discussion and your input would greatly inform the development of the causality assessment tool.

We appreciate that you have many competing demands on your time. However, we hope that you are able to spare the few minutes necessary to ensure the success of this important project. Ms. Coombes will contact you by telephone in the next few weeks to determine your interest in participating in our study and to arrange an interview time that is best suited to your schedule. Please let us know if you do not wish to participate and do not want to be contacted by telephone.

If you have any questions, or would like to discuss our research further, please do not hesitate to contact either of us. We hope that you will accept our invitation to participate in this important research initiative.

Very best regards,



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Appendix 4: Bracketing Activity

These are a composition of reflective notes on causality assessment in early phase oncology clinical trials.

I personally have had no experience with cancer, clinical trials, or assigning causality. I have however, had personal communications with individuals who have been involved in oncology clinical trials. Working with the Canadian Cancer Society, as a hospital oncology volunteer, I have sat and talked to several individuals diagnosed with cancer, while waiting for their treatment. They have shared a variety of experiences with me including treatment regimes, symptoms, and changes in quality of life. However, all of these conversations gave me a patient perspective on the matter, and none of the experiences were related to attributing causality.

In performing a literature review, I have gained insight on the pre-existing empirical data on attributing causality in early phases of oncology clinical trials. It is evident to me, that the process of assigning causality is not perfect, and that there are many issues with this phenomenon. I go into this data analysis knowing that this process is full of inconsistency and constraints, that there is no standardized method to assign causality, and that error is inevitable. However, to the best of my abilities I will set aside these preconceived notions, in order to allow myself, as the researcher, to truly enter into the world of the interviewees and gain a true understanding of the essence of their experiences, gathering a holistic sense of the phenomenon at hand.

Appendix 5: Findings Summary Table

Grey/Problem Area	Coping Strategy	Potential Consequences
Lack of Resources		
No training	On-the-job training	Inconsistency in reporting standards
No tool	Placing a strong emphasis on strength of association, use investigators brochure	Inconsistencies between professionals in terms of causality assessment
Lack of resources	Rely on their experience	These professionals are uncertain of their causality attribution expectations
Vague definitions	Rely on their experience	Uncertain causality attributions
Communication issues: <ul style="list-style-type: none"> • Interviewees and sponsors • Physicians and patients 	<ul style="list-style-type: none"> • Search for additional resources online, consult with other investigators • Try to get to know their patient on a personal level 	<ul style="list-style-type: none"> • Difficult to reach a unanimous decision • Inaccurate representation of adverse events from patient
Uncertainty of the Job		
Assigning Causality (Patients are in the advanced stages of their disease, numerous treatments, complicated medical histories, etc...)	Consider protocol drug, dose response rates, temporal association, patient history; accept that there is a grey area, reevaluate attribution at a later date, get to know patient, use their clinical experience	Erroneous causality attribution; difficult to determine if the developing agent is indeed working.
Subjective Judgment and Experience		
Inter-professional subjectivity	Rely on experience, do extra background	Reaching a unanimous decision becomes difficult

	work to familiarize oneself with agent	
Patient subjectivity	Ask probing questions	Inaccurate representation of adverse events, can lead to unattributed adverse events, or over-attribution
Apprehensive Causality Attributions		
Under attributing causality	Err on the side of caution	Risk patient safety
Over attributing causality	Learn to better understand the drug under development	Scrutinize agent under development, ineffective treatment schedule
Competing Goals		
Sponsor/Pharmaceutical company pressures	Keep patient safety as priority	Causality attributions may be questioned by the sponsor/pharmaceutical company
Drastic timelines	Rely on one's experience	Rushed attributions, unconfident decisions
Internal pressures <ul style="list-style-type: none"> • Patient pressures • Research team pressures 	<ul style="list-style-type: none"> • Keep patient safety as priority • Use best clinical judgment 	<ul style="list-style-type: none"> • Under attributing causality to the drug being tested • Conformed causality attributions

Appendix 6: Horizontalization

Significant statements were extracted from the transcribed interviews and made easily identifiable by attaching key words (meaning notes)

Extracted Statement	Meaning Notes
So there's often not a lot of guidance it's more winging it.- S01	No Guidelines Intuition
Yeah, and I would say timing is the most important factor. I mean, other factors, we don't usually have dose as a, as a ah, we don't usually have doses in the same, different doses in the same patient to be able to judge a dosing relationship- S01	Dose Relationship Temporal Relationship
Certainty is very difficult to achieve- S01	Uncertainty
I think that the probable, possible, etc scale is better, it just gives more room for interpretation of the interpretation.- S01	Interpretation Coping with Uncertainty
Yeah and yes and no is desperately frustrating sometimes because things are grey like, you know, if it's unlikely but it's still possible then saying you know, is that yes or no because that's hard.- S01	Frustrating Interpretation Grey Area
There is a lot of background noise in side effects, what side effects may be caused by other drugs, disease.- S01	Difficult Decisions Uncertainty
As previously mentioned dose, you know, often we don't have a dose relationship that we can look at.- S01	Patient Confusion Lack of Resources
Supposedly one of the criteria for causality is something like a dose response relationship whereby more of something causes more of an effect. And a patient typically, although we may have that in a cumulative dose, we don't have different doses from cycle to cycle necessarily. So you can't say when you had a little bit of this you felt a little nauseated, now that we're giving you 10	Dose Relationship Lack of Resources

times more you're feeling really nauseated. So we wouldn't have that information typically. - S01

I think it can interfere, the inaccuracy of it can interfere with drug development and can potentially in the most extreme case, kill a drug. Or I suppose on the other side allow a drug to go ahead when side effects are overlooked. Although if, if you have a bunch of us who are calling unlikely things possible, because you know, we're not really sure because it's just subjective. And the FDA looks at that or the investigators look at that and decide, you know we just have too many pulmonary embolisms and they're all possible, as opposed to unlikely, you know, it can impact what they do with that drug. They may change the dose and lose effect or they may stop the trial or whatever. So there's risk to the drug and to the patient.- S01

Subjectivity
Over Attributing
Under Attributing

I don't know that I have, I think, I can certainly imagine however, in one's own trial whether there's going to be a bias and you don't want side effects to be attributable to your drug, um. [like if you were the PI] Right, if you were the PI easy to imagine and it may or may not be conscious though. And on the flip side is you may have a prejudice against the drug because it is prior reputation, or difficulty of administration or something which you know. I can't say that personally in short I've felt anything in particular, but it may be lack of experience to date.- S01

Bias
Subjective

But we're still stuck with you know, these vague situations with the problems we've discussed and I don't, it's not clear.- S01

Uncertainty

Most of it is kind of intuitive you know, so I'm not sure.- S01

Intuition

Um, sometimes it's grey, you know, maybe could be and that's the difficulty.- S03

Grey Area

And, and ah, um, what really annoys me is when investigators at other sites don't pay attention to this and let's say there's an SAE they attribute it to you know, very likely study drug.- S03

Annoying
Lack of Attention

if it's done incorrectly, it's a pain in the ass for all the trial nurses and all the invest, all the trial doctors all over the world because it takes time to sort out.- S03	Frustrating Consequences of Misattributing
My head.- S03	Intuition
Just my clinical judgment.- S03	Clinical Judgment
My common sense.- S03	Common Sense
Well if you have, ah, ah following the patients with this and it takes how many minutes or hours to do it, it's very costly [it adds up] it's very labour intensive.- S03	Workload Time Constraints
And the ICH/GCP guidelines which this is part of is, is, ah, is making it very, very difficult to do this sort of research and it's unfortunate because you know, we need to study new drugs, we need to, yeah.- S02	Difficult Impedes Research
Yeah, you know, my concern is sometimes not enough attention is paid or they don't understand sometimes what the implications are so they don't give it enough time, they don't understand it.- S03	Lack of Attention Times Pressures
I mean it's almost from the experience we've had with drugs.- S03	Experience
From a causality point of view, I mean there's more stress if the adverse event is of a more serious magnitude in terms of determining how related it is to the trial medication.- S04	Stress
And I think a lot, a lot of that has to do with you know, how do you make the decision, it's difficult sometimes, sometimes it's pretty straight forward that they're experiencing an adverse event that is know to occur with the study medication.- S04	Difficult Hard to Assign Causality
Actually not any that I know of.- S04	No Resources
So I think, those ones are okay because you're basing it a bit on personal experience [yeah] and a	Personal Experience Intuition

little bit on what's published.- S04

I can't say that there any actual guidelines that I know of or that I specifically follow.- S04

No specific guidelines

So it's more like each case, hopefully, you know, the fear is that you're not consistent I guess, that you know, you're scoring a patient differently, that's, that's the fear.- S04

Fear of Being Inconsistent
Patient Safety

There's, there's two concerns, I think one concern is you know, over assigning causality. Because patients are, they can get sick, morbidities, multiple medications, actually a lot of reasons and it sometimes it's easier to blame it on the drug. But I think my fear is that if you, if you do that liberally you'd be, not discrediting the drug but you're not um, it could lead to dose reductions, could eventually work their way into an ineffective treatment schedule for that. If you saw a whole bunch of side effects that you thought were you know not really related to the drug and that led to that drug being less .- S05developed in a certain disease. Maybe you're doing a dis-service to that patient population, so that's one, that's one concern I have. Perhaps over-assigning causality just because of the complications of some of the patients on the program is my biggest concern. And the other concern is, the other, completely opposite really is the not assigning causality and then drugs are allowed to develop. And then it's only when you start getting into Phase 2, Phase 3 studies that you really, adverse events really show themselves. And you're thinking well why wasn't this picked up in the Phase 1 or 2 studies? [yeah] So I think you can go either way, you can make errors on either way, one way you might kill a drug that might be successful and on the other way you might let a drug develop not carefully enough.

Fear of Over Attributing
Fear of Under Attributing

I mean the biggest stress, not that I've had any stress about it, but the biggest issue is assigning causality that could result in a Phase 2 program going to a lower dose or something like that or you know a ineffective dose for a given cohort of patients is a concern, whether you're doing the,

Concern of Over Attributing

you made the call because that's often a critical step in a clinical trial.- S04

Oh, very little, I mean I think um, a lot of the pharmaceutical sponsors that we did some studies with, had some training modules but not necessarily for causality mostly for adverse event reporting- S04

Little Training

I normally don't use anything particularly that formal.- S05

No Tool

There you're getting, you're, you know it's hard to, to, how, how strongly are you going to implicate the study on the side of implicating the study drug just from these issues.- S05

Over Attributing
Difficult

I think yes or no becomes very hard and we're not always sure you know. And there's always that element of doubt about it. But I think you have to be able to say how strong or weak your doubt is and when you have the graded scale it just gives you some flexibility to do that.- S05

Doubt
Uncertainty

Yeah, they are really, I think in some cases we have to be, make sure that well, is there an element of doubt but clearly that's where the unlikely category comes in and these are patients who are being said, well it's probably related to their targeted agent and you know, clearly that's probably likely not the case. But what that does is it really contaminates the whole database in terms of what is the causality of these toxicities. It's a huge problem worldwide and we certainly see that when we're having to look at data from large international studies where you have groups who probably don't have a lot of experience with either the chemo or the targeted agent. And making these attributions it really kind of make a mess of the database.- S05

Over Attributing

There's an awful lot of pressure when you're doing early phase studies with a small biotech company. They, there's a lot riding on, on, you know, there are the issues of well are you going to torpedo their only drug or just from a financial point of view, with toxicities that are going to expand the dose level.

External Influences
Time Pressures

That's gets in and take longer for the study to complete, those have big financial implications. On the other hand our, our first responsibility is to the patient and if not I think making sure, a lot of pressure from the smaller companies. And I think the other pressure is just the sheer volume of the adverse events you know, here are the ones from the last couple of weeks. So it's just huge volumes and they all, and everybody wants them done within kind of 24/48 hours and it just becomes impossible to do. On some level there needs to be, and a lot of these are these ones that you know it's clearly the chemo drug and probably really isn't related to the study drug. But there's, probably half of those are those kind of things that have been generated, probably inappropriately because of the experience of the people who, it's a problem. It's a huge workload and unless we're handling them consistently I'm not sure we're going to be any further ahead.- S05

There hasn't been any formal training, yeah, there's hasn't been anything formal.- S05

No Formal Training

That is a challenge in that typically when patients go in to clinical Phase 1 trials they have advanced, often refractory cancers and ah, needless to say, significant ah, medical problems at the beginning and throughout the clinical trial.- S06

Challenging
Confounding Variables

Basically all one can really do is, based on experience of managing these people sort of know what to expect as their cancers progress and as their regional stages of life, as in previous experience in managing.- S06

Prior Experience

It's really based on experience at this, at this stage. So really it would depend on a, an experienced investigator who has managed a lot of the specific patient population to in my opinion, accurately determine if this is something that's related.- S06

Experience
Subjective

No I'm not aware of any.- S06

No Tool

That's a clinical judgment based on what's happened to the patient.- S06

Clinical Judgement

I think it's better to maintain a sort of a graded scale because I don't think one can be that definitive. With the number of resources you have, it's only a matter of being able to document and have there as a possibility.- S06	Uncertainty Grey Area
Um, I would say that more resources would be good for investigators, more resources at their disposal. [what sort of resources] Well, resources through the sponsor [for what] for information [oh okay] more information as to whether, you know, if you have questions about a certain event. And for example you wanted to understand the drug's pharmacology better and try and determine you know, in some way could there be access to that information beyond the IB. The opportunity to discuss on a regular basis with other investigators, how the trial is going, um, through conference calls is a good idea.- S06	Lack of Resources Disconnect with Sponsors
Um, well there, you know, there, I think one has to fight, now this is a more of a perception, I don't have any examples. But there's a risk that the sponsor may want, may prefer you to go to an unlikely conclusion. That I disagree with.- S06	External Pressures Sponsor Pressures
No I haven't because I've stubbornly just said well that's my final answer, so I've never felt any, any sense of coercion. Obviously, you know, inherently results in more work for somebody but ah, in the Phase 1 setting I, I, I think ultimately it's the sponsor's in their best interest to fully understand what their drug is doing and what it's potential effects are. But one does have to be fairly stubborn in that regard.- S06	External Pressures Strict Decisions
Lack of appropriate information.- S06	Lack of Information
Well I think if there's a, I think there is a certain distance often between the clinical trials nurse and the physician.- S06	Lack of Communication- Clinical Trials Staff
So it is experience.- S06	Experience
The challenge is that the good Epi group who can	External Pressures- Drug

run trials in an academic setting are going to be approached by drug companies. And you need a lot of money, those staff have to be paid and there are costs to the clin epi group and that's a lot better than a local academic.- S07 investigator say getting a grant for 100,000 bucks and he can give you a \$1000 bucks. I think they're, they're, the risk I think comes in the academic setting when the institute needs to kind of step up I mean today that's being done, certainly here's its done so it's, but I don't know about other centres across the country.- S06

Companies
Financial Pressures

No not really, using just yeah, anything.- S07

No Guidelines

Well usually there's teleconferences and other meetings to discuss what's happening with other patients. But a lot of times communication isn't as good as it could be.- S07

Lack of Communication-
Communication not up to
par

We should be involved in as much of those discussions just so everybody is informed. I haven't done a lot of, so I don't know what they do to keep it up but sometimes you do feel a little bit, you have no idea what the other people are doing. And it would be a little insightful as to how they're doing it, yeah.- S07

Feel Lost
Disconnect from other
Professionals

Problems, first of all you're never definite, definite, hindsight's always 20/20, so looking back a few months later you can sometimes get a more clearer picture of what, like analyze the situation a little bit more. Sometimes when you're right in the situation and you have to, you have that responsibility of assigning it right then and there, you don't have all the information right? You don't know how it's going to end, you don't know, um, if, if, why it happened or anything. You can analyze the situation after it occurred and everything has evolved then it's sometimes easier to go back and go well this and this happened we can do that. So assigning causality sometimes at the time is sometimes clear cut and sometimes very difficult.- S07

Uncertainty
Time Constraints

Why, because you know what, um, it's those minor things that can cause good quality of life issues in patients.- S07	Concern for Patient Concern for Minor Reactions
Not too much, but then again I'm not the one that the sponsors contacting when they call you and go are you sure that this is what you think it is? and stuff like that. I've had one of those calls where they'll call back and they'll say is this the way you want it? And you just go back to the physician and tell them they want to reconsider. And sometimes the physician is, will stick to their guns and sometimes they will re-think it or whatever.- S07	External Pressures- Sponsor Pressures
Oh, who knows, whenever you get an algorithm it's always like the yes/no's sorts of things and sometimes there's a grey in-between. So sometimes you have to kind of think differently.	Grey Area- Change Mindframe
But it's also insightful to know how the patient feels and how their quality of life is, is affected as well.- S07	Concern for Patient
Nothing formal. Sometimes in start up meetings or something like that they'll, they'll say a little blurb about assigning causality but they won't really give like formal education as to what, we should use this tool or anything like that. It's mostly a set reaction sort of.- S07	No Formal Training- Learn from Experience
Well I think it's based on what's been listed in the protocol and possibly the investigator brochure. But really do you have time to look at an investigator brochure every time? No.- S08	Time Pressures
Mostly I find you know I tend, I agree with, with the conclusions they come to and sometimes um, I think there's a tendency to over report disease-related symptoms as being related to the investigational agent by the invest, you know, to be reported by the investigator. - S08	Over Attributing
And so in that setting there's a discrepancy between what the investigator feels and what the medical monitor feels. - S08	Over Attributing Conflict

And then you have, because different companies will approach it differently and so then you have AstraZeneca with their reports. The company sort of reports basically they, they want to downplay um, these and so their stock standard line is that you know, such and such a side effect is not listed in the investigator brochure, the implication being well it can't be related. So you know they take the, so you've got to look at it with, it's somewhat helpful but somewhat tedious. - S08

External Pressures- Drug Companies

No, cause what happens, they'll send us the report and then it's up to us to how we deal with it. I mean they have to be forwarded to the REB and the internal documentation that we do is more about sort of thinking for ourselves whether we want to make consent changes. Whether we see something which is happening you know, with um, severity or a frequency that would justify making a change to the consent form. And that doesn't happen very often, in part because you know, we tend to wait for, because periodically there will be an update to the investigator brochures and then they'll considered if the consents need to be updated. - S08

External Pressures

Sometimes in some places for some companies you know the serious adverse event would be mucositis, diarrhea and dehydration. And other places and I guess the NCIC in particular, I mean our recent experience, is that they say well the drug doesn't cause dehydration, the diarrhea and the mucositis does. So you have primary adverse event and then you have secondary effects from that [right]. And then really only want the primary event reported as the serious adverse event and then what's secondary to that is covered in the description of the serious adverse event. - S08

External Pressures- Drug Companies

S08: [that's a bit of a challenge] It is and some of that is sort of developing a better understanding of what individual sponsors want or expect. But on the other hand maybe there should be you know, greater consistency. - S08

External Pressures- Varying Sponsor Expectations

M: You find that there is variation among the sponsors as to what it is that they want and expect.

-

S08: Yeah.

Imprecise science! I am not, I mean I guess to have definition, I mean more clearly defined sorts of definitions of the terminology would be most, would be the thing that would be most helpful. [which terminology?] You know, in terms of the causality terminology, so more clearly define what people mean by unlikely, possibly, probably, you know definitely related. And at least people are using the terminology you know, in a similar fashion. - S08

Unclear Terminology
Inconsistency

Well I think that there are, I mean I think you know, if you start sort of labeling a drug as having you know x, y and z side effects and in fact they're in fact they're side effects related to the disease then you know, um that's a problem. But on the other hand does it, how does it limit development of the, the agents. I'm not certain, well I'm not less certain that it's going to limit development of the agent. - S08

Over Attributing- Seen as
Problem

No, no I'm not aware of any.- S09

No Tool

Yeah, I mean you use your clinical assessment and um, and it's really process of elimination and if nothing else comes out.- S09

Clinical Judgment

You always look at, I mean there are always so many other confounding variables in this population, especially if their disease is starting to get a bit worse. They go on other medication, right which can impact, you don't know what these newer agents do with any of the other medications that are out there. There are just so many variables that can [yeah] affect, drug-drug interaction you know and drug-disease interaction, drug-foods. I always make a point of asking patients are they on any over the counter or complimentary therapies because they may not think, well I'm not taking any medication but they're on all these herbal or [yeah] just lots [lots of unknowns right?].- S09

Uncertainty
Confounding Variables

Well, I think you can overcall things that, and say

Over Attributing-

that they're related when they're not. [mmm hmm]
Um, and then that leads to for the drug companies to sort out or, or you know, whoever the sponsor is in determining are these or are they not? And I think um, it would be beneficial at some point to follow through on the other end of things to see what it means when you're on that end. [what do you mean on the other end?] Like a CRO getting this information in and saying now, you know, oh well what does that mean, the word, how you take it and what did they do with it from that point. Because I mean we submit the information but what happens on that side, but I think.- S09

Consequences for Drug

I think it would be beneficial for all of us maybe to spend a bit a time with them and see. Or even with the data management, I don't know what they do with the data management part of it. [yeah] And I think it would help us understand part of what we're doing too when you see how companies or CRO's try to collate the...- S09 information we send to them. And then what it can do in terms of, you know analyzing the study or management part of it. [yeah] And I think it would help us understand part of what we're doing too when you see how companies or CRO's try to collate the information we send to them. And then what it can do in terms of, you know analyzing the study or.- S09

No Resources
Lack of Communication
Disconnect with Drug
Companies

Um, well they come back and say well are you sure that's related? [mmm hmm] right [yeah] you know. No I'm not sure but I'm not willing to say it's not, you know.- S09

External Pressures

M: Sort of the pressure to keep the drug development process moving I guess.
S09: Um, hmm, um, hmm. Yeah, very much so. And, and I think some of the pressures come around too is you know to put patients on study and sometimes that feels more, that's more the goal rather than the safety of the patient. I think we rely on the companies to monitor these studies and when they don't, especially the early phase studies, and when they don't there's a huge problem with that. I'm not perfect, and they're not

External Pressures- Drug
Companies

either but I think they then have the responsibility to monitor those studies and get those forms back into data management so they can make the proper queries that will probably, that could correct anything that you're not even aware of.- S09

I'll be honest and say I don't really have any [really]. I don't have any tools that I use.- S10

No Resources

I like the scale because yes/no is pretty black and white and often there are many scenarios where you're just not sure.- S10

Uncertainty

I think the biggest implication would be that if a drug gets attributed to have a set of adverse events that are quite serious then that may preclude further study of that drug, that might stop the trial. And if you're looking at a dose escalation study where you're escalating to your next dose based on the tolerated dose, you're now saying that there's some side effects. Well you might not go to the next dose level, or you're recruiting more patients to that particular cohort level so subjecting more people to the drug than may be necessary in a clinical trial. So the issue of not, of a potentially very good drug not being taken further because of the concerns of the adverse events, that's going one way. And the other way if you don't attribute the causality, a potentially dangerous drug could come to market without the proper, or with concerns about adverse events.- S10

Over Attributing
Under Attributing
-Concerns of...

Often these patients are just, have such complicated histories, you know, they're prone to other medical problems.- S10

Uncertainty

Well I think just the fact that there, there isn't a systematic way to do it, that it often is based on hunches and feelings as opposed to a rigorous method or measurement tool.- S10

Hunches & Feelings
Intuition

Well if you're involved in industry studies then certainly there's some pressure from, not so much for assigning causality but continuing. So if you've had someone who has had an adverse event and you want to dose reduce them or hold off treatment

External Pressures- Keep
the Drug Development
Process Moving

for a little while sometimes there is that pressure to continue with the study. So in that sense you could think well maybe if you had assigned them a possible as opposed to a probable relationship then you could, you could be pushed to continue with the study. But you always have to keep the patient's safety in mind [right] at the end of the day so, so that's what you go by.- S10

But I must admit I really haven't had that much pressure in terms of treating the patient. It always comes down to the patient's safety and that's what you go by.- S10

Patient Safety- Priority

M: And then um, do you know of any tools that are available to help in assigning causality? Have you every used any sort of a decision tree or an algorithm or [no] something like that? No. [no] Do you think that would be useful?

S11: I do think that would be useful um.- S11

No Tool- But would be Useful to have one

A lot of the times I find it's hard and I don't think it's an on purpose thing from patients, but I don't necessarily think that we do get every single bit of information all the time.- S11 [yeah] I think different things are reported to different people, depending on your position, whether that be chemo nurse, clinical trials nurse or the physician.- S11

Missing Information
Lack of Resources

So I think it definitely depends, again, very individual, depends on the patient, depends on your personality, what you're asking. If you're asking the appropriate questions or not, I think that that makes a big, a big difference too.- S11

Personality
Subjective

Oh gosh, it's hard to say, again, every patient is different. Some patients, um, some patients I think it's easier to leave everything open and let, just leave it as a blank slate, let them tell you everything that's been happening. Um, some patients if you do that won't tell you anything. So some patients, not prompting but some patients you need to I think go through a list of questions and ask them about specific side effects, problems, even possibly body systems and leave it open that

Individual Variation
Subjective

way for them to suggest things to you. Um, again, um, I find it's, again reporting is very different from person to person in terms of the clinicians.- S11

Um, and again I think that's very subjective for the clinician also the way the patient describes things. I could consider it a grade 2 whereas the physician could consider it grade 3. - S11

Subjectivity- Patient & Clinician

Again, I'm not really sure that's optimal especially considering how, you know, little time everybody has these days.- S11

Time Constraints

Um, I mean to start out with the very basics, a lot of, a huge workload involved, um, in doing it poorly and that, I mean it could be anything. Just from the workload involved in SAE's, even the reporting, all the different avenues it needs to go through.- S11

Workload

Um, an implication could be the fact that drugs aren't being marketed or aren't moving on to different phases of trial because causality has been improperly assigned. It could also on the very opposite side of the spectrum, it could also lead to harmed patients, it could lead to death in patients. A whole array of things, I mean it could obviously affect the statistical analysis of the study, it can affect everything.- S11

Over Attributing
Under Attributing

Who's kidding who, they're busy and overworked, um, and trials are a lot of paper work. So I think that's possible, I certainly don't think there would be malicious intent [no] but I, but I do think that you know, even time constraints that sort of thing could have, play a factor in that.- S11

Workload
Time Constraints

I've had no formal training [no] actually.- S11
So if, if, there's an SAE that, that comes out of that, that has So if, if, there's an SAE that, that comes out of that, that has implications for notifying sponsors, the sponsor notifying the regulatory agencies and the company, there's timelines for doing so. The nature of enough AEs may influence the conduct of the study [how does it influence?] so misrepresent, well a series of SAEs may [9:51].- S12

No training
External Pressures

<p>So you could in one situation attribute something to an entire one set of the, the most serious and if it's this and you don't acknowledge it, that's dangerous for future patients in the study. [right] If it's, if it's you know, this and you label it as this, you could be potentially closing a trial that presumably was well thought out and had a good hypothesis and the hypothesis could end up being rejected. [implications] Potentially [yeah] I mean if you polarize the extremities yeah, most of the stuff is not going to end up being that extreme, it's going to be in the middle but.- S12</p>	<p>Under Attributing Over Attributing</p>
<p>It's just very practical and if ah, I mean there is a bureaucratic process that is time consuming that if you assign an SAE versus not that somebody's going to have to do a lot of work and meet timelines and set a whole ball rolling.- S12</p>	<p>Time Pressures Bureaucratic</p>
<p>I think you then have the issue of the sponsor, and sponsors, sponsor may influence. [okay, how so?] I think in general from what I've seen, sponsors will tend to, tend to things that are expected, the, if the consequence is an expected one and it's tended less to be labeled serious adverse event even if it's expected but the degree and the severity wasn't, that's a tricky one, you give an agent.- S12</p>	<p>External Pressures- Sponsors</p>
<p>I have to admit that is very subjective at times.- S13</p>	<p>Subjective</p>
<p>Um, well to be honest, not really I think you just go on what your best clinical judgment is or what your patient's status is.- S13</p>	<p>Clinical Judgment</p>
<p>None. [no] No, well I mean, I guess I shouldn't say that, none in terms of standardized criteria that's for sure. Resources, unless you mean basically going back to see maybe the investigator brochure and trying to understand some of the toxicities.- S13</p>	<p>No Tool- Nothing Standardized</p>
<p>Well there's definitely implications in serious adverse events, and, and association, obviously if</p>	<p>Over Attributing Under Attributing</p>

you put it wrong then there's misinformation. If it is associated and you don't think it is then that, that's probably the more harm there because we need to be aware, particularly in Phase Is that we need to be aware of and people think oh it's very unlikely I'm going to put it not related but then obviously that's information that the physicians and the patients in particular need to know about. So I think the worst is an association that is there but one grades as not associated and, and harm could be done to patients. The other extreme is people, and I see this a, a lot because you have to, as the PI on the trials you have to signoff on all the REB submissions to the REB. People that put everything is associated creates lots of paperwork. Where its very clear in reading through their SAE this was not drug related, this was disease related. And to me that doesn't do any harm to patients which is good but it creates extra paperwork for the CRAs, for the nurse, for us, for the REBs and to me that's more irritating when it comes from all around the world, you know you get. [yeah] People could be, could think a little I think, I don't know, think a little bit more clearer in terms of what they think is associated and perhaps those that are not associated would save the.- S13

But ah, um, you know, I think it's a very subjective process, that's the problem. And subjective in terms of ranking them or associating but also subjective in how much effort people actually put into the work. And I won't say I do it all the time but you know, I think in terms of how much background work one does in trying to understand the causality with each one trying, if you're not certain, if you are certain it's very easy. Perhaps, if you're not certain are you going to spend that extra time to pull out the IB or talk to you're you know, pull out the protocol and actually do the best.- S13

Subjective
Effort Levels

So unrelated, definite, possible. Like what's the unlikely and probable versus possible versus probable, you know, where do you draw the line? Again, it's very subjective.- S13

Subjective
Inconsistent Scale
Measures

But ah, um, you know, I think it's a very subjective

Uncertainty

process, that's the problem. And subjective in terms of ranking them or associating but also subjective in how much effort people actually put into the work. And I won't say I do it all the time but you know, I think in terms of how much background work one does in trying to understand the causality with each one trying, if you're not certain, if you are certain it's very easy. Perhaps, if you're not certain are you going to spend that extra time how much background work one does to pull out the IB or talk to you're you know, pull out the protocol and actually do the best [7:30].- S13

Subjective

The challenges are particularly in Phase I trials these are, these, they all have their advanced disease, they often all have been through numerous other treatments, some of them have been heavily pretreated. Many of them are not of the greatest performance status and so they have a lot of other co morbidities or symptoms that can merge and play a role. Sometimes these brand new drugs we really don't know. We don't have a lot of information, that's why we do the Phase Is. And how much weight we put on what is seen or not seen in dogs or monkeys or whichever animal work they have done it on, large animal work done, kind of you know, there's not a lot of data there, so in the end if you don't have a lot of data to work with and you have patients, it does become very hard.- S13

Uncertainty
Confounding Variables

I mean I think um, basically um, if we all had more time in our day it would probably be easier to do it. The SAE has to be filled in within 24 hours. I mean that's another issue, why 24 hours? what's the urgency? By the time we receive it, we send it off to the sponsor, it goes to REB, there's going to be a lag time anyways. And you don't expect things to, you know, maybe grade 5 toxicities where you have a death, maybe that should be 24 hours. But I, I don't know why an SAE can't be 48, so you don't feel that pressure to have to. Not that, I think we do it just because we feel a pressure, but again I think we just said 24 hours and that's just been the rule that's been adopted all along right. [right] I actually don't see the rationale of 24 versus 48.-

Time Constraints
Disconnect

S13

Well I think the only external pressures is obviously be accurate as possible. And so you know we're part of the, part of the Princess Margaret Consortium and you know a couple of the NCI trials, you know the NCI physician from the US is emailing me in terms of causality, so obviously there are pressures to be as accurate as possible. But sometimes you really don't know if it's associated or not.- S13

External Pressures-
Accuracy

Yeah, [yeah] yeah I think so. [okay why?] Well because there's a, it may help you sometimes in the dilemma where you in this grey zone of serious adverse event where you think about what to, what to assign to this SAE. If you have a clearly unrelated or clearly related SAE that's easy but the, the vast majority of SAE's is probably somewhere in between..- S14

Uncertainty
Comfort in Grey Area

But that is basically based on, on the situation and your experience and not on any formal rules or algorithms or whatever.- S14

Clinical Judgment

Well you can clearly overlook, worst possible thing would be that you actually don't report a side effect which is actually a side effect, from, from the drug. That may really happen, but I think one of the existing problems is that the frequency of those side effects maybe under reported.- S14

Under Attributing

Overlooking it altogether is certainly worse [yeah] but I think [it's also important] a serious adverse event, if a serious adverse event is seen in relationship to this more often then at some point we, we report it. But I think the frequency may then be under reported. But the key, overlooking a side effect or not reporting a serious adverse event which is actually part of the side effect profile, that's probably the worst, the worst thing.- S14

Under Attributing

The opposite is true too, if you , if you report an SAE which is not related to the drug [mmm hmm] then that can cause a considerable, can have considerable sincere consequences for the, for the

Over Attributing- Serious
Consequences

drug and the development of the drug.- S14

Worse case scenario that you delay or you stop the development of the drug. I mean imagine that a patient dies on a Phase I study and you assign the death as possibly related to the study drug and it wasn't. Something like this can kill, kill a drug in the development or at least considerably delay it or cause a lot more costs for the, for the company or whoever develops the drug to do additional testing and stuff like this.- S14

Over Attributing- Serious Consequences

Well it's so subjective, in the end, for the majority of SAEs which are in this grey zone of possibly or likely or unlikely related, it's a very subjective, a very subjective thing.- S14 which is based on experience and, and of, of the investigator.- S14

Subjective Grey Area

No, not that I'm aware of, not that we use here that I'm aware of.

No Tool

Um, probably the sponsor wanting an answer right away of what the cause, because sometimes you don't know, it's hard to make a decision on one patient, like the first patient that presents. Especially if that particular patient has multiple problems and it's possible that it could be their disease or a component of their disease that's causing the symptom or the, the abnormal lab result.- S15

External Pressures- Time Constraints

Um, well, of assigning them poorly? It's either you under, or whatever event it was so you're compromising safety of future patients who might go on this treatment if you um, rule that it wasn't related to the drug. Or you might over, you know if you say that everything is related to the um, to the investigational drug then you're over, over rating it as to whether the drug is causing problems. So it's pretty serious.- S15

Under Attributing Over Attributing

Well the potential ramifications of that is the drug might not go out to market and it might be a potentially legitimate drug. [okay] Because describe SAEs or have SAEs that might not really, that are manageable or might not really be 100%

Over Attributing- Ramifications

related to the drug. Especially if you pick a poor group of people who you know always get admitted for nausea and vomiting because they have a poor ECOG status. And it could be that they were just very poor patients initially to put on treatment.- S15

Um, more information from the sponsor I guess in terms of um, side effects of the drug.- S15

Lack of Information

The first issue is how quickly can you really assign it? Often you know, you need to report within 24 hours. Within 24 hours you may report, the person came in with chest pain, da, da, da, and you don't have any real idea if it's related or not.- S16

Time Pressures

I think there's two big concerns. One is if you assign causality and say it's related improperly then it might tarnish a good drug and stop dose escalation in a way that wouldn't be appropriate. Alternatively if you ignore it, it might cause further toxicities in others and be potentially dangerous to other patients. I think it's a very dangerous thing. I also think that sometimes as oncologists we tend to minimize rather than maximize because we're used to toxicity with drugs and that can be dangerous.- S16

Over Attributing
Under Attributing

I think sometimes, sometimes you're in such a rush to get the CRF done that I think you don't necessarily spend enough time. And I think one of the other problems is we get so many reports about drugs, you know like alerts [safety letters?] safety letters that sometimes everybody doesn't know these things and may not know if it's related or not. I think keeping up with the safety letters is hard, [just because you get so many of them?] mmm hmm and not really knowing the drug well.- S16

Time Pressures
Not Enough Time

The timeline, it's mainly the timeline and the pharmaceutical company.- S16

Time Pressures

I think most of the doctors who do a lot of clinical research are aware of the fact that you don't want to underestimate the toxicity of a drug. But at the same time you don't want to assign every single

Under Attributing
Over Attributing

adverse event to the drug some will not be due to the drug. So you usually end up in the, this is a possible to probable consequence of the drug if it's in the grey area where there could be many reasons why the patient had an adverse event.- S17

One always worries if an investigator who is on, perhaps working with a drug company may wish to minimize adverse events because they really want this drug to be a success or acceptable. And it need not necessarily be driven by egregious opportunities around receipt of research funds, it may be because they get sort of um, too invested in the drug itself and wanting it to succeed or wanting their career to succeed or something of that nature. But that can induce investigator bias. Um, on the other hand you can have some investigators who um, will always attribute causality to the drug because they rather simplistically think if anything bad happens it must be the drug.- S17

Under Attributing
Over Attributing

Are there tools out there? [laughter] no I don't. [okay].- S18

No Tool

You know, where the same event can be attributed differently because a lot of things, it's a subjective assessment. It's not as objective as it should be, I think that's what makes it a challenge.- S18

Subjective
Lack of Objectivity =
Challenging

Um, I think any time with an investigational agent, like I said your antenna are fairly high up and you probably are more likely to ah, to lean on the side of, you don't want to harm a patient or subject to harm to assign causality where it may not have. Like assign a higher level of attribution even if it may not have been. So you know, when in doubt the diagnosis of exclusion is going to be that it's, it's the investigational agent. [yeah] So, and that may be unfair to the agent under development right. [mmm hmm] So it's just your level of, you scrutinize it more, like I said a more conservative approach to when in doubt, better to say it's possibly related than not. Those are, and no tool.- S18

Over Attributing
Hesitant

That's where I think issues of attribution become very difficult.- S19

Uncertainty

I think it's human nature to forget things [okay, forget] and obviously if it's a very serious event, it's going to be recorded and you're likely going to hear about it in some way. But not all patients understand that in a clinical trial that we're also interested in the side effects of the treatment. And in a Phase I actually toxicity is your primary endpoint. [mmm hmm] But the patients of course feel that they're on the treatment to help their cancer [yeah] so there's a little bit of a disconnect there. So they're more interested in what the drug is doing for their cancer and they kind of are hunkered down with the idea, many of them are very stoical right [yeah] they say I'm going to put up with whatever side effects I have to put up with um, to get through this treatment because it's going to help my cancer. And I think that's, that translates sometimes to a lack of reporting of events. I think that some patients may also perceive that you know, the doctors or nurses don't want to hear them complaining right, they just feel that they'll sound like whiners right.- S19

Lack of Information
Patient Bias

And if you're so busy or have not done your homework in terms of reading about the drug, or don't have the time to go look it up. So you know, basically just having a busy clinic and being busy at work can lead you to mis-attribute these things right.- S19

Workload
Time Constraints

Third parties, um, our CRA's sometimes want things attributed in a certain way.- S19

External Pressures

Yeah, I was just thinking they're, when you look at attribution of adverse events, I mean they're basically the people you're working with [yeah and they want] you think you're filling out a CRF and then um [they] they want an attribution level. And ah, sometimes they have their opinions about what the attribution is and they're different from [yours] mine. You know, not a lot but um, that just in terms of explaining to them and then they have to change

External Pressures
Workload

their forms [yeah, yeah] and if they've already submitted the forms a certain way. Ah, in affect you're creating more work for them, ah, so that does, I don't like to create more work for the people I work with. So I do feel a little but of pressure there, but ah.- S19

Besides the patient, family members, maybe differences in behaviour, maybe some psychologic or neurologic issues associated with the medication because we just don't know enough about them, ah lab work, imaging results sometimes [okay] and the physical examination.- S20

Lack of Information
Lack of Communication?

No. I think we basically use our medical judgment and the sources of information.- S20

Clinical Judgment

But you have to, I think you have to assume that you don't know enough about the drug that it could be drug related.- S20

Uncertainty
Err on the Side of Caution

I think a lot of it sometimes is the background noise from patient or the disease. And how do you know the symptoms are not related to the cancer or to underlying symptoms from other comorbidities from other chronic diseases the patient may have? - S20

Uncertainty
Confounding Variables

Well sometimes it's difficult, somebody, say somebody with chest pain who has plural metastasis it's really hard sometimes to know whether this is related to pulmonary embolism. Then basically have to do the appropriate diagnostic imaging which in that case would probably be a spiral CT scan to try and sort some of that out. Um, what other symptoms? say patient fatigue, ah, well that can be really difficult for instance, it could be related to disease, study drug, could be related to psychologic factors, some change in the patient's environment, who knows? And that could be, and you have to look at all those and figure out which is most likely and then it's you know, and have there been changes in those areas that might explain it? Um, and if there's more than a couple of possibilities you have to kind of use your judgment which is more likely.- S20

Difficult
Uncertainty

I guess, I guess one of the biggest challenges these days is that if we, people have enough time to rigorously evaluate all the possibilities in a very busy clinic setting. [yeah so] The time to sit down and really fully go over everything with the patient in terms of what's new by history and do a good physical examination.- S20	Time Pressures
Um, I think everybody's under severe time pressures these days and it makes it, it's um, you need to have a dedicated infrastructure to do good Phase I and II studies.- S20	Time Pressures
Nothing formal.- S20	No Training
No, it's kind of, for me it's like an intuitive process, and I should also say that sometimes the CRA's do it.- S21	Intuition
Just that there's more than one possible explanation for a lot of toxicities that you see. So as you say, PE can be due to the drug or it could be due to the cancer and maybe they would have had that PE even if they weren't on the drug or because they're immobile or any number of factors. I guess it's just that there are multiple factors at play. I'd say that's the most difficult aspect of it. And plus the fact that they may be on other treatments, like they may be on something for their hypertension or their diabetes [yeah], they've got often multiple medical problems aside from the cancer.- S21	Uncertainty Difficult
I probably don't give it as much thought as, as I should. I mean, I guess the real risk is that if people are falsely ascribing SAEs to the drug when it's really the cancer then you could potentially throw out a good drug.- S21	Over Attributing- Risks
And I guess the converse is true too that if you don't, if you don't adequately report the toxicities then you might be introducing a drug to the market that is dangerous.- S21	Under Attributing
Yeah, that's a very valid question, sometimes I will	Internal Pressures- Patient

have a patient who is having a serious toxicity and I want to stop the drug and the patient is pressuring me to keep on the drug. And you know, if you are going to keep them on the drug then maybe you have to under report the toxicity.- S21

No, I don't, I don't think so, no, it's mainly the example I can think of is patient's pressuring me to keep them on a drug when I'm not sure that's to their, you know in their best interest.- S21

Internal Pressures- Patient

Zero.- S21

No Training

I guess, I keep coming back to this, but keeping it simple and brief because there are a lot of competitors for a trialist's attention, you know, like there are a lot of time constraints and something more simple that would be best.- S21

Time Constraints
Need for Simplicity

And then it becomes difficult for me, but then you're forced to make some kind of a decision.- S22

Difficult

To the causality [oh the causality yeah] because you have to react in some way. So I had to think this morning for example this ocular side effect, was it due to you know, drug A or drug B or the combination. Or was it due to something incidental like you know conjunctivitis or something. So you have to think about alternative causes, alternative explanations. I mean people with cancer get many symptoms from the cancer that are not necessarily due to the drug, they may just be due to the underlying disease. And of course a lot of people have comorbidities because they're elderly and have a 101,000 things wrong with them. And you know, is it just something incidental. So I think one of the important things in the causal reasoning is, is to be aware of what the possible causes could be. You know, it's due to the experimental drug, it's due to some other drug the patient may be taking or may have just started taking. It could be due to the underlying cancer, it could be due to some other illness that may have occurred or that may have already existed like diabetes or angina or something you know. So I think critical in the sort

Uncertainty
Conflicting Alternative
Attributions

of, the kind of cognitive approach is the realization that there's a whole slate of things which could possibly either alone or in combination have resulted in this phenomena.- S22

On the other hand you don't want to be paralyzed by uncertainty because if you're in a busy clinic you can only tolerate paralysis for so long [right] you have to make some kind of a decision.- S22

Time Constraints

But every now and then it's tough, like what happened this morning for example, it was difficult, it wasn't clearly obvious to me what was going on.- S22

Difficult

You might argue you know, causality is difficult, causality is not simple. [no] You know, there's different kinds of causality, there's the kind of relationship where something is sufficient on it's own. [right] There's another kind of relationship where something by itself is not sufficient on it's own but it's necessary. [and then there's] And there's relationships that are where you have it's neither sufficient nor necessary but it nonetheless contributes. So it's actually, on the one hand you're saying well just attribute causality but there's actually a more profound and fundamental understanding of causality with respect to well what type of causality? Um, which is important I think because it does help you manage the situation you know, so sometimes I don't think it's possible to be 100% sure.- S22

Difficult
Uncertainty

You know, this is caused by drug X or it's not. And in a sense I don't like that because, I know, I just don't think it represents the reality and the reality is sometimes there is an element of uncertainty.- S22

Uncertainty

But, but even if you stumble on a strategy that's effective it doesn't necessarily mean that there aren't other strategies that are also effective. [sure, yeah] So this just speaks to the complexity of this, especially when you're dealing with two drugs.- S22

Complex

M: So definitely dealing with two or more drugs in

Challenging

combination is a challenge [yeah] in terms of assigning causality, are there any other challenges? - S22

Well I think you know, they have to make a judgment in a hurry, so there's a concern straight away, they're on the busy machine in the clinic and they have to, you know, somebody puts some form in front of them and they kind of, you know, they've got two pens, one pen in their left hand and one pen in their right hand and they're hitting the typewriter with their nose and looking at the screen and trying to do four things at once and the telephone is ringing and so on. It really is a zoo as you know, so they have to make hurried decisions, so that's my one, that's my number one concern.- S22

Time Constraints
Stressful

Um, I think it's a long way from engineering right now and I think a lot of it is gut feeling and kind of intuition.- S22

Intuition

But it may not be quite that easy to do with chemotherapy, even in the, even off trial, but it's particularly difficult to do that on a trial because you know that you might sabotage you know, the intent of the study by just unnecessarily stopping. You know, I think the onus on an investigator and somebody who's responsible for treating the patient on a trial is quite high really because they have the ability to undermine the trial by making a fallacious attribution. You know because something might have happened you know, they got gastro because they ate something at some restaurant or something and then you say well it's the drug and you take them off the drug. Well then you undermine the whole enterprise you know which isn't just that trial, it stretches back over probably 15 years of work and money and investment. And it's so easy to undermine it by making, by casually making the wrong attribution.- S22

Over Attributing
Difficult Decisions

So there's two kinds of mistakes you can make. You can make a false positive attribution or you can make a false negative lack of attribution, when

Under Attributing
Over Attributing

in fact you should have.- S22

So it's, you know, these things are in a way matters of life and death, they can be.- S22

Serious Decision

And I think a lot of things can happen under the, under the banner of uncertainty. You know, you can be forced to under, I think that uncertainty is at the heart of this, its at the heart of this. And I don't think it's a matter of honesty or dis, I think it's uncertainty and how do people cope with uncertainty? And I think that this actually is the measure of whether enterprises succeed or fail. You know, it's how they deal with uncertainty. So I think for example one of the differences between successful businessmen and unsuccessful people in business is that the unsuccessful people don't know how to deal with uncertainty. Um, because life is full of uncertainty and you know, it's possible to be panicked into, into making a wrong decision. On the other hand it's also possible to be paralyzed into not making any decision at all. [yeah] So when you see these kind of little human dramas played out in this situation as well because, but I think it's a mistake to not allow the physician to be uncertain when he or she is genuinely uncertain.- S22

Uncertainty

The real, the really difficult issue is where you would have a situation where you would have to stop the study drug or reduce the dose of the study drug. There I think it becomes particularly difficult and particularly important that the correct decision is made. If you're simply going to say well you can treat this with a bit of Imodium or some heparin or something it doesn't really matter. But where you're forced to interfere with the conduct of the study and the administration of the new drug that's where it becomes acutely important to do the right thing.- S22

Over Attributing
Pressure to Be Accurate

I have seen situations where some pressure, let's say that the pharmaceutical company maybe had a different viewpoint about what was said, you know without being specific I've certainly seen that. I think most people have, most people that deal with

External Pressures-
Pharmaceutical Companies

pharmaceutical companies realize that they're obviously coming from a certain angle. And that they may have a different interpretation, sometimes, I think sometimes they're right. I think, I'm not saying they're always wrong but certainly they have a viewpoint [sure] which they express you know.- S22

I think you know, if a patient is sick in a way that taxes the resources of the cancer center and the hospital, I think you know, there's certainly pressure not to carry this on beyond what's reasonable. And you know, that's, that's understandable and inevitable.- S22

Internal Pressures

Well more so but there was a lot of problems with some of the toxicities as well, all the patients were having serious adverse events. But they were also very ill patients and it's very hard to separate that out at times.- S23

Difficult Decisions

Time, the physician's time.- S23

Time Pressures

Well it's the companies they want to get their drugs to market and sometimes you get a little pressure from them you know? [to do what?] Well to just to confirm yes this is related particularly if it's nasty, nasty stuff. There's a couple of companies out there that don't think twice about picking up the phone, you know, asking you to review with the physician, that's fine we'll review it but ultimately we're not here for the trial. Well we're here for the trials, but we're here for the patients and so we're not going to cause them any harm if we can help it.- S23

External Pressures-
Pharmaceutical Companies

Minimal at best [okay] basically on-the-job training. I think all the CRAs we basically self-train or train each other as we go.- S23

Minimal Training

Yeah, um, yeah, obviously we haven't received any training for it but um, I'm not sure that we're the ones who are actually expected to come up with that determination. - S24

No Training

Nothing in particular pops up, I mean I can see

Uncertainty

there are some areas that obviously are a little grey as to which way the assignment should go, whether it's definitely related or somewhat related.
- S24

Grey Area

So the physician meets with the patient [mmm hmm] and afterwards they come out and they dictate what sort of went on. [mmm hmm] And often times it's not extremely detailed, is that what you're saying? - S24

Lack of Detail

Lack of time probably. [just time pressures, yeah, okay that would seem reasonable].- S24

Time Constraints

Um, ah, well just that, that, it's always, you never know whether something, there could be that chance that you don't know whether something could be related if it's a new event if it's happening with our patients.- S25

Uncertainty

Yeah, more detailed information I guess, other than what's in the consent form, having a list of expected events and maybe, some of them put in the percentages of what the patients have already experienced. So yeah, I guess that, just a more detailed sort of, um, like I was saying we go to the dose modification and it will list sort of what the expected toxicities are and the rules to follow. So maybe to have some kind of I don't know, chart or information in that area to go to, to see what we're looking for and how they expect us to assign the causality.- S25

Lack of Info
Lack of Communication-
Expectations

Yes I guess, um, I was going to say something similar to that, that they might be making decisions quickly without really going to source, some sort of source or really knowing.- S25

Time Constraints

Um, well I find the companies, well they don't always agree and then ah, [with your assessment?] with our assessments. And you see that often in safety reports that come through, it's tends to be always a possible or probable assessment when it really may not be necessary. But not a major pressure other than they want to know what the causality is you know, with that

External Pressures
Time Constraints

initial, if it's an SAE for example [yeah] they want to know that right away because they have to send that out to other sites. [yeah] So you know, that's the pressure there to sort of um, get that answer quickly. And because we don't want to make that ultimate decision they may be getting our assessment initially that might not be the correct one so I guess that would be a concern or a pressure for me [yeah] to get the physicians ultimate decision on [right]. Because they want the information quickly right with an SAE so.- S25

Ah, yeah, they could do that for sure, they might phone us, or during monitor visit they might um, sort of query it and ask questions about why we, thought it was related or not. And then give us their reasons why they think it should be different and want us to change it and we might not always want to. So there's, there's always that happens, usually they would speak with the physician, we'd have them speak directly with them so they would discuss their reasons for their assessment. But it does happen.- S25

External Pressures
Question Decisions

But other than that um, as far as education as to how to assess the causality [yeah] I would say that's really minimal to none.- S25

No Training

Well I guess one of the things that I've always had a difficult um, thing to grapple with is that there are too many, often there are too many categories of relatedness. [okay] You know, like definite, probable, possible, unlikely or not, do you see what I mean? [yeah] And I think that those are fairly subjective definitions that will vary from person-person. You know, what I think is unlikely is not necessarily what you might think to be unlikely [mmm hmm] and so um, again the assigning of causality there could be sort of chance depending on the interpretation of the definition by the individual physician.- S26

Subjectivity
Confounding Variables

Ah, none [can you recall a time?] none really, I mean there's, the only pressure that you feel um, is the sort of sense of urgency of, because you know you have to fill out the SAE report within 24 hours

Time Constraints- Make for
Difficult Decisions

and all this sort of stuff. You may not have all the information and you may make an original, you may make an assessment that subsequently you change or becomes clearer as time goes on that something else is in fact happening and you want to change your mind about something. Which is, which is fine and you do, do that but I think that sometimes, I don't know that you should necessarily have to assign the causality right away. I mean I think reporting the SAE right away and saying this is what's happening and we're monitoring the patient and these are the steps we've taken. And we'll, you know, as things evolve we'll let you know what we think actually happened, rather than saying yes we think this is study drug related within the first 18 hours when you don't, you may not necessarily have all the facts yet.- S26

Well as I said I think sometimes it's arbitrary and it depends upon the physician's interpretations of the definitions of you know, these different things. I think it depends a little bit on the physician's past experiences, expectations and biases with respect to the class of agents and so on.- S26

Subjective
Arbitrary

Like I think that whole 24-hour, like I understand that we need to report the event but I think the causality part of it should be delayed until after you have the facts. And then you can say okay really I think this is you know.- S26

Time Constraints

Trial and error I guess. I mean the only, the only lecture I've ever heard about is, I've heard A speak once, but other than that you know, really nothing. I mean you'd ask other more senior investigators what they would say for this particular event and so on. But otherwise, there was no formal training.- S26

No Training- Nothing
Formal

Well I guess just trying to determine which drug could be causing the adverse event, you know if it's, you know they could both be causing it, it could be one or the other so you need to do.- S27

Uncertainty
Multiple Variables

And pre-existing conditions in the patient if they

Uncertainty

<p>have you know, other health problems that could be contributory to some symptoms. You know, and sometimes it can be as easy as just the person themselves, some people will say they're perfectly fine when they're not. And other patients will elaborate on you know, how they're feeling and might be exaggerating a little bit. So you know you have to try and understand the patient themselves as well.- S27</p>	<p>Patient Subjectivity</p>
<p>Well, most of my studies are also sponsor studies and they tend to make the wording vague on purpose. [laughter] Probable, possible [the wording of what] probable, possible, definitely related, possibly related all the, so sometimes that can be a challenge if it's something you haven't encountered before.- S28</p>	<p>Lack of Information Disconnect with Sponsors</p>
<p>So anytime they asked for anything to be changed I would leave those queries up to him and 9 times out of 10 he would not change them. [oh that's good] Because, but then it gets annoying and then you start to second guess and wonder why are they even asking if the investigator is ultimately responsible for the data and not some data entry person a million miles away who has no idea what is really going on. Why are they second guessing this, what are they really after?- S28</p>	<p>External Pressures Annoying</p>
<p>So quite often I think it can be multi-factorial, it may not be just due to the one thing [yeah] so it's complex, pain is complex. So I don't think you can, sometimes it might be obvious, I mean if someone has bone mets and they come in and they have a fracture. That's pretty straightforward, it's their disease, but it may not always be that straightforward.- S29</p>	<p>Uncertainty Pain- Subjective</p>
<p>No. [no eh, you don't use any?] No, in fact I think people tend to lean towards putting it, like when they're not sure, and most people are never 100% sure, they'll say you know either probable or could be. And I think we see a lot of "could bes" more than any other.- S29</p>	<p>No Tool Err on the Side of Caution</p>
<p>Well we probably don't pay as much attention to it</p>	<p>Lack of Attention</p>

as we should. I mean a lot of the initial information is prepared by the CRAs or the study nurses and I think in a practical everyday busy clinical environment we have these things coming across our desks to be signed almost on a daily basis. And I'm not sure if we think about it as much as we should, if we give it as much attention as we should, because it's just another thing to be signed. [mmm hmm, yeah] And there's been sort of very little attention paid to it in sort of the clinical research area.- S29

Like pain, pain is subjective, fatigue is subjective, I mean you can try and quantify it but if you think that the study, that the causality, that fatigue is due to the study drug you're not going to have objective evidence. [true] Weight loss, well I guess if you have weight loss you can measure them in pounds but it's not always going to be there.- S29

Subjective
Not Always Objective
Evidence

Because I think you can falsely label a drug with all sorts of um, toxicities that have nothing to do with it.- S30

Over Attributing

So it's really, it's, there's, it's a combination of factors when you're making decisions, when you're designating causality.- S30

Uncertainty

Um, and it can go both ways, if you only see a very small number of patients you may underestimate or under-relate particular symptoms to, to the drug. And the same thing can also happen where if, if you just decide that every bad thing that happens to a patient is going to be possibly attributable then, then not only do you jeopardize the development of a drug but you also, those things all get added to patient consent forms and they muddy the waters for patients.- S30

Under Attributing
Over Attributing

Well with smaller drug companies you tend to get more queries about why did you assign this as attributed or not attributed? You know, what do you think the underlying pathophysiology is? and so you know, smaller drug companies particularly when their entire livelihood depends on, on a single agent will, will be, will, I don't know if

External Pressures- Drug
Companies

pressure is the right word but they will definitely discuss extensively how and why you've chosen that something is related.- S30

So sometimes there are grey areas and at the time it might be difficult but retrospectively by continuing to look at data after the fact then you're able to um, to decide at a later date.- S31

Uncertainty
Grey Area

It's tangible evidence that there is a toxicity. But something that is not a direct result but could subsequently happen is I think a grey area, and it could probably, it might have been, we don't know for sure. [yeah] So that's why I say it's kind of a grey [yeah] a grey area.- S31

Uncertainty
Comfort in grey Area

So you're assigning causation when maybe it's not it may be something else. So as a company I think they're obligated to list that as a part of their um, their package. Maybe not, maybe they don't take into account certain timeframes. Maybe they have a tool.- S31

Over Attributing
Timing

No.- S31

No Training

It would have been nice if we could have established causality unanimously but. [yeah] So I say going to the physician but if there is more than one involved there can be more than one opinion.- S31

Subjective

So sometimes it's hard to attribute it to exactly one specific thing. You kind of have to say it could be a combination of their con-meds and their study medication and the chemo, so it's harder to give a causality. So usually a lot of times we just, we have to answer unknown because we're not, we can't specify exactly, possibly, could be related you know.- S32

Difficult
Uncertainty

A study drug that may have that same adverse effect. So trying to directly relate causality to that sometimes is difficult when you know that it could be experienced in two, two different, or three different medications.- S32

Uncertainty
Difficult

But when it's subjective, like how a patient is feeling or how sore their mouth is or you know, how much pain they might be experiencing, it's all very subjective to each patient. So severe to one person might be you know, moderate to another. So those kinds of things I find, unless you can assign a number value to it I find that hard to grade. Because some things are very subjective, pain, those things are, in my, I find personally hard to grade.- S32

Subjective- Patient

There's no formal training really, you just kind of got thrown into the position.- S32

No Training

Note: S= Subject

Appendix 7: Clustering Meaning Units to Form Themes

Units of Meaning	Themes
No Guidelines (3) Uncertainty (31) Grey Area (3) Confounding Variables (1) Difficult (14)	Coping with Uncertainty
Personal Interpretation (1) Intuition (4) Subjective (13) Clinical Judgments (6) Common Sense (1) Personal Experience (5) Hunches and Feelings (1) Personality (1) Individual Variation (1)	Subjective Judgments
No Guidelines (3) Unknown Dose Relationship (3) No Resources (9) No training (13) No tool (7) Lack of Communication (4) Unclear Terminology (1) Lack of Support (1) Missing Info (1)	Insufficient Resources
Fear of Under Attributing (14) Fear of Over Attributing (24)	Apprehensive Causality Attributions
Time Constraints (24) External Pressures (25) Internal Pressures (3) Workload (4)	Competing Goals
Frustrating (2) Patient Confusion (1) Annoying (1) Lack of Attention (4) Stress (1) Inconsistent (1)	Non-Redundant (Incorporate throughout)

Feel lost (1)
Concern for Patient (3)
Serious Decisions (1)

Appendix 8: Transcript Characteristics

Interview	Center	Position	Specialization	Time
Subject 01	JCC	Medical Oncologist	Lung	22 Minutes 24 Sec.
Subject 03	JCC	Medical Oncologist	Breast	31 Minutes 31 Sec.
Subject 04	JCC	Hematologist	Blood (Lymphoma, Myeloma)	26 Minutes 39 Sec.
Subject 05	JCC	Medical Oncologist	Gynecologic	22 Minutes 26 Sec.
Subject 06	JCC	Hematologist	Melanoma, Non-Hodgkin's Lymphoma	24 Minutes 27 Sec.
Subject 07	JCC	Clinical Trials Nurse	Hematology, lung	24 Minutes 47 Sec.
Subject 08	JCC	Medical Oncologist	Breast, lung	29 Minutes 04 Sec.
Subject 09	JCC	Clinical Trials Nurse	Breast	38 Minutes 10 Sec.
Subject 10	JCC	Medical Oncologist	Breast, GI	24 Minutes 31 Sec.
Subject 11	KRCC	Clinical Trials Nurse	Hematology	38 Minutes 40 Sec.
Subject 12	NCIC	Hematologist	Hematology	29 Minutes 3 Sec.
Subject 13	BCCA	Medical Oncologist	Breast, head & neck	18 Minutes 20 Sec.
Subject 14	BCCA	Medical Oncologist	Gastrointestinal, genitourinary	24 Minutes 28 Sec.
Subject 15	BCCA	Clinical Trials Nurse	Ovarian, lung, breast, GI, head, neck, melanoma	22 Minutes 55 Sec.
Subject 16	BCCA	Medical Oncologist	Breast	22 Minutes 55 Sec.
Subject 17	BCCA	Medical Oncologist	Breast, lymphoma	25 Minutes 45 Sec.
Subject 18	BCCA	Medical Oncologist	GI	22 Minutes 14 Sec.
Subject 19	LRCC	Medical Oncologist	Unknown	46 Minutes 18 Sec.
Subject 20	LRCC	Medical Oncologist	Unknown	38 Minutes 32 Sec.
Subject 21	LRCC	Medical Oncologist	Unknown	29 Minutes 34 Sec.
Subject 22	LRCC	Medical	Unknown	54 Minutes 03

		Oncologist		Sec.
Subject 23	LRCC	Clinical Research Associate	Unknown	25 Minutes 40 Sec.
Subject 24	ORCC	Clinical Research Associate	Prostate	31 Minutes 30 Sec.
40Subject 25	ORCC	Clinical Research Associate	Unknown	40 Minutes 37 Sec.
Subject 26	ORCC	Medical Oncologist	Lung	37 Minutes 21 Sec.
Subject 27	ORCC	Clinical Research Associate	Head, neck	34 Minutes 43 Sec.
Subject 28	ORCC	Clinical Research Associate	Lung, ovarian	30 Minutes, 58 Sec.
Subject 29	ORCC	Medical Oncologist	Breast, lung	34 Minutes, 20 Sec.
Subject 30	ORCC	Medical Oncologist	Colorectal	31 Minutes 41 Sec.
Subject 31	ORCC	Clinical Research Associate	Brain, breast	36 Minutes 54 Sec.
Subject 32	ORCC	Clinical Research Associate	Breast, GI	29 Minutes 29 Sec

Appendix 9: Memoing

Subject 01

S01: So am I going to get a consent form for this?

M: Laughter, yes, you just signed it remember and then threw it in your recycling bin? [oh right yeah] So let's start, so even the most experienced clinicians find assigning causality to adverse events challenging. And many groups, such as industry sponsors, clinical trial cooperative groups and research ethics boards they all expect prompt and sensible causality assessments. But, assigning causality is not straightforward and if done poorly it can have large implications for patient safety and drug development. So what we're interested in doing is developing a tool to help clinicians efficiently and reliably assign causality during Phase 1 oncology trials. And we feel that by better understanding your needs as a clinician we can make our tool more relevant to you the clinician. So have you got any questions before we start? [No] No, okay great. So let's say one of your Phase 1 clinical trial patients has just reported experiencing an adverse event. Can you please walk me through how the situation is handled?

S01: So you gather whatever details you can and I think with any side effects you're thinking about you know, general issues of causality such as you know, a temporal association with the taking of the medication. **(Pays attention to timing)** Is this something that is mechanistically plausible from what we understand of the drug? Is it something that has been previously reported or associated with the drug from the investigators brochure or whatever information is available through the trial. And so you just try to gather information around that and then it's a best guess.

M: So what sort of, when you say temporal association, what is it that you're sort of looking at?

S01: Ah, are there any, you know, was the medication taken, the experimental medication taken prior to the adverse event? Were there other agents, ah, experimental or otherwise that were taken concurrently with that? So did the patient get an experimental agent plus some sort of standard chemotherapy that may also be implicated? Or were they taking other over the counter medications or prescribed medications that maybe, may offer an alternative explanation and started at a similar time.

M: So what are the resources that you refer to when you're assigning causality?

S01: I mentioned the investigators brochure or the protocol itself, mostly looking at prior side effects and mechanism. You know, if the patient has hemoptysis and is on an anti-ontogenesis drug and you know, you're, you're more likely to accept. Um, I suppose occasionally colleagues would come into play asking if they had seen a particular side effect, it would be less common. I, you know, any literature that may already exist is kind of overlapping the other sources but you know if you've read any trials or abstracts related to the drug that indicates side effects previously seen.

M: Are there any tools that you use to help you when assigning causality?

S01: No [no] like, no, I don't think I'm even aware of any tools. [no, okay]

M: And would you use one if one was available?

S01: If a tool was not cumbersome [yes] yes then it would be.

M: What sort of general guidelines do you follow then when you're assigning causality? You run through all these sort of gathering the details and

S01: Yeah, I mean I don't have, in, in kind of the literal sense I don't have a guideline set, that I refer to you know. I've been, protocols actually, typically it's not that explicit as it is to what to look for except for timelines, up to 30 days after last taking a drug or something. So there's often not a lot of guidance it's more winging it.

M: Do you think the protocols could be a little bit more helpful that way?

S01: Yeah, I guess so, if they could be helpful.

M: What do you consider to be the most important factor when assigning causality? Temporality?

S01: That's probably the strongest, the strongest of the factors. [yeah] Yeah, that would outweigh mechanism which we often don't understand, you know, other drugs which. **(Not a lot is known about protocol drugs)** Of the alternative explanations still I think you have to give the benefit, we tend to give the benefit of the doubt to the experimental agent as being the, being toxic or being the adverse agent.

M: You tend to err on the side of caution and ascribe it to the experimental drug.

S01: Yeah, and I would say timing is the most important factor. I mean, other factors, we don't usually have dose as a, as a ah, we don't usually have doses in the same, different doses in the same patient to be able to judge a dosing relationship. And sometimes we're in a position where you stop the drug and re-start it and you get a repeat occurrence of the drug so that kind of reinforces the temporal association.

M: I would just like to ask you now to consider the following scenario. [okay] Let's say you're treating a 65-year-old female patient who has a confirmed diagnosed,

a confirmed diagnosis of metastatic breast cancer. And she's in a Phase 1 clinical trial with a new investigational drug and she experiences a pulmonary embolism. How would you assign causality to the study drug if there was a 75% chance that the adverse event was related to the study drug and a 25% chance that it was related to other factors, such as adjuvant treatment, disease progression [are you asking on that little cause of probably, likely] Yeah, if the categories were certain, probable, possible or unlikely.

S01: I would put it as probable. [probable] Certainty is very difficult to achieve.

M: When would you use certain?

S01: Um, I think, if, if I, you know, certain things are more obvious like a pulmonary embolism is just something, as you mentioned, a common cause of metastatic disease, chemotherapy administration. But a rash for example may, a peculiar rash may you know, without other new drugs being started may be more associated or something else, well rashes aren't rare but um. So probably something up around you know 90/95% I would consider it to be sufficiently certain in human terms to call certain for a trial. [yeah] Now 80% I would still say is probable.

M: How about if there was a 50% chance that it was due to the study drug and a 50% chance it was due to other causes or factors would it still?

S01: I would call that possible. [possible]

M: And what about if there was a 20% chance that it was due to the study drug and an 80% chance it was due to other factors?

S01: If the other categories underneath possible are unlikely and not?

M: Certain, probable, possible or unlikely.

S01: Um, so 20% chance [mmm hmm] oh, that's tricky I think I would still call it possible. [yeah, okay] I would stick unlikely may be down around 5 or 10% but I don't know.

M: So given the choice, would you prefer to grade causality as certain, probable, possible and unlikely or as a yes related to the study drug or no not related to the study drug.

S01: I think that the probable, possible, etc scale is better, it just gives more room for interpretation of the interpretation. Look at a series of adverse events and see how people judge them and get the general impression from, you know, from that information about, about where to go. If you read a clinical vignette about a patient, you can get an impression and make an assessment like I did. But if you're the clinician who is taking care of the patient and has even more detail and maybe a more accurate gestalt then I think you can assign a slightly more accurate value. **(A closer relationship to a patient yields more accurate causality attributions)** It may be um, you know, it may still be incorrect but it's going to be probably a little bit better. So it, it let's you see what they saw or it gives you their impression second hand, I think it's better. Yeah and yes and no is desperately frustrating sometimes because things are grey like, you know, if it's unlikely but it's still possible then saying you know, is that yes or no because that's hard. [right]

M: What would you say are some of the challenges or problems with assigning causality?

S01: We don't know mechanism often. There is a lot of background noise in side effects, what side effects may be caused by other drugs, disease. Um, temporal

associations are often surprisingly difficult to tease out and you sometimes cannot be sure that the onset of symptom was actually after drug administration.

M: Why is it difficult to tease out?

S01: patients can sometimes be unclear or maybe our questioning is unclear but they have so much going on that something that may have been a minor nuisance or low grade symptom that suddenly becomes more evident. You know, it's also difficult for them to tell I think sometimes, if they've you know, felt a little tired and achy but they had a couple of other side effects and some anxiety that was masking that. They might not realize that until you know, afterwards, symptoms change over time and so it can be unclear to the patient. Um, what else? [concerns, problems when assigning causality] As previously mentioned dose, you know, often we don't have a dose relationship that we can look at.

M: What do you mean when you say that?

S01: Supposedly one of the criteria for causality is something like a dose response relationship whereby more of something causes more of an effect. And a patient typically, although we may have that in a cumulative dose, we don't have different doses from cycle to cycle necessarily. So you can't say when you had a little bit of this you felt a little nauseated, now that we're giving you 10 times more you're feeling really nauseated. So we wouldn't have that information typically. That's all I can think about right now.

M: What are your concerns about how clinicians currently assign causality?

S01: I think it can interfere, the inaccuracy of it can interfere with drug development and can potentially in the most extreme case, kill a drug. **(Concern for protocol drug)** Or I suppose on the other side allow a drug to go ahead when side effects are overlooked. Although if, if you have a bunch of us who are

calling unlikely things possible, because you know, we're not really sure because it's just subjective. And the FDA looks at that or the investigators look at that and decide, you know we just have too many pulmonary embolisms and they're all possible, as opposed to unlikely, you know, it can impact what they do with that drug. They may change the dose and lose effect or they may stop the trial or whatever. So there's risk to the drug and to the patient in each way of misestimating. [any other concerns] No

M: What external pressures from third parties have you felt when assigning causality?

S01: I don't know that I have, I think, I can certainly imagine however, in one's own trial whether there's going to be a bias and you don't want side effects to be attributable to your drug, um. [like if you were the PI] Right, if you were the PI easy to imagine and it may or may not be conscious though (**Feels that PI's want to drug to succeed**). And on the flip side is you may have a prejudice against the drug because it is prior reputation, or difficulty of administration or something which you know. I can't say that personally in short I've felt anything in particular, but it may be lack of experience to date.

M: From your perspective, what would make assigning causality easier?

S01: When you gave me the percentages I realized how poorly I estimate. How I had not considered the relationship between the terms and the percentages. And that might be an improvement, giving numerical ranges, at least we'd all be speaking the same language, I think, although maybe even that has difficulty. Um, I guess I'm not being very creative at the moment but I can't think of [no that's good] I can't think of tool that would make it easier. I mean we have a list and most of us have been in a class somewhere where the, you know, some of the elements of causality have been discussed so we know kind of what we are

looking for. But we're still stuck with you know, these vague situations with the problems we've discussed and I don't, it's not clear.

M: Maybe just making that a little more systematic.

SO1: Yes or, in a, yeah, no point in suggesting research but [or what] well no, I don't know, I think, could one go and look back at, at these factors that we're talking about, you know, temporal association, dose, other um, other factors, competing factors or explanations. Could you actually go back and look at a series of SAE's and see how those are, which of those played the greatest role. And ultimately based on what happened to the drug in the future, which of those was the best criteria to rely upon. [hmm] I don't know. [that's a good idea, cool]

M: What I'd like to do now is just give you a list of 10 questions that were developed by a researcher named Naranjo, and I don't know if you're familiar with Naranjo's algorithm to help clinicians assign causality to adverse events. So what I would like if you could just carefully read the questions and cross out any that feel are not relevant to the Phase 1 oncology clinical trial setting. [okay]

S01: I think they're all relevant, two are a little bit more difficult, number 7 was the drug detected in blood in concentrations known to be toxic. That's not always going to be feasible. And 10, was the adverse event confirmed by any objective evidence, I'm not sure what that means. If that means, was the PE pulmonary embolis you know, diagnosed by a VQ scan or pulmonary angiogram. We aren't really sure what the adverse event was what that means exactly. But otherwise it all seems relevant.

M: You're thinking objective evidence means some sort of imaging or something is that right?

S01: Yeah, I guess so, was the adverse event confirmed by any objective evidence. Adverse event, if it's a rash, how are you going to confirm it, you see it. Pulmonary embolism, you do an image so I'm not really clear what they mean. I mean if we call it an adverse event, I think we typically use some sort of objective measures, it seems redundant. I shall strike it off, good-bye. [get rid of it]

M: Okay, so now would you be able to just rank the remaining questions then in order of importance to assigning causality. [okay] So 1 would be least important, 10 would be most important

S01: I only have 9. [that's okay] Okay, a little bit arbitrary but, because some things are not too dissimilar to importance I think. So a lot of the temporal stuff here for example, did it disappear, did it, sorry, was it temporally associated, did it go away when we stopped the drug and did it come back when we re-administered it. They are all kind of the same temporal category, but they're all, they add something each I think.

M: Okay, did the reaction reappear when the placebo was given, you ranked that as 3.

S01: Yeah, I think that, I mean, it's important, it just doesn't happen that often, just like detection in the blood. You know, typically in a phase 3 study it's not going to happen so in terms of what's most relevant and practical I would say that you're not going to be able to give somebody [in a Phase 1 study] and you don't know the placebo typically. [right] So it's, it's nice, but I wouldn't want to have to, you know if I was trying to, if I was thinking about a tool then it's just not practical, it doesn't happen so I would get rid of it. [yeah, in this situation you wouldn't need that] Right. And the other thing, item 7 detected in blood [so what's the problem with that one] in, in a Phase 1 study and say higher doses and you would run into dose limiting toxicity. But in a Phase 2 or 3 study you probably don't have blood levels, unless you meant this to be explicitly Phase 1.

M: Yeah, well we're thinking, yeah, Phase 1 primarily and

S01: The other thing is some patients have you know some patients get reactions to drugs that are really uncommon. So it wouldn't surprise me if some patients could get reactions at lower concentrations than other patients. So we'd find, you know, and we'd still be left with, well you know maybe you're particularly sensitive and we don't really understand a lot of that stuff so I would still rank it probably where I did as the weakest.

M: And are there any questions on here, like anything that was missing that you think maybe should be added or anything come to mind that you think oh that's not in it at all.

S01: No, I don't think any of the things I mentioned in the discussion were outside of that, we just did some of it.

M: So lastly I would just like to ask you a little bit about your experience as a clinical trial researcher. So in which cancer(s) do you specialize?

S01: Ah, lung normally, I've done some head and neck as well and here I'm doing GI but that doesn't happen till next week. [okay, so not a lot there]

M: So you have a Bachelors, like you have MD right [yes] and what year did you get that?

S01: 96.

M: And do you have a Masters or PhD [no] or anything? And when did you get your medical oncology license?

S01: I guess, I didn't get a license to independent practice until, I mean I've had resident's licenses for a long time but I, 03.

M: And what year did you become involved in clinical trials as a researcher?

S01: I guess it would be 01.

M: Overall, what percentage of your work time would you say is devoted to clinical trials?

S01: 50%?

M: And what percentage of that is devoted to Phase 1 or 2 clinical trials?

S01: Probably, most of it's Phase 2 so 35%, I mean, of this [yeah, of that 50] of that 50% [yeah] 70% [70% of that time and then the other 30 would be Phase 3] Phase 3 yeah.

M: Have you ever been a local PI?

S01: Yes. [yeah okay]

M: And have you received any other training?

S01: Do you mean local PI as in here locally or just [no because you just arrived here right] right [so in your experience as an investigator] yeah, right

M: And can you tell me about any training that you've received specifically with respect to assigning causality?

S01: Nothing formal. I did a Trials Fellowship at the NCI Canada but it would just have been incidental, nothing formal.

M: When did you do the Trials Fellowship?

S01: 01 to 02 [that was at NCIC] yeah.

M: And so what did you learn in that, like did they actually talk about causality?

S01: No, it was just incidental nothing formal.

M: So you just sort of had to teach yourself along the way or?

S01: Yeah, you know, reading protocols, writing protocols, seeing what was in there.

M: What additional education about assigning causality do you feel needs to be made available to clinicians?

S01: I don't know that the list that was just given, imagined list or whatever, most of that, most of that I think we've seen and have a sense of so I'm not sure how much education would help with the accuracy. Most of it is kind of intuitive you know, so I'm not sure. And if there was to be a session, probably 5 minutes would be enough just to say you know, remember these are the criteria and to maybe, to better define you know, likely, unlikely, possible.

M: Great, so those were all the questions I have, is there anything, oh the last thing is there anyone else you recommend that I speak to. I don't know if you, you just started here so have you.

S01: Yeah, probably no one that you haven't already had contact with.

M: What about, have you, you haven't started any trials here have you [no] because we're actually would like to speak to clinical [no I don't have one yet] you don't have one yet. Great thank you.

Subject 03

M: Even the most experienced clinicians find assigning causality to adverse events challenging. And many groups, such as industry sponsors, clinical trial cooperative groups and research ethics boards all expect prompt and sensible causality assessments. But, causal, assigning causality isn't straightforward and if done poorly can have large implications for both patient safety and the development of new drugs. So we're interested in developing a tool to help clinicians efficiently and reliably assign causality during Phase 1 oncology clinical trials specifically. And we feel that by better understanding your needs as a clinician we can make our tool more relevant to you. So do you have any questions about this before we start? [No] No, okay great. So let's say one of your Phase 1 clinical trial patients has just reported experiencing an adverse event. Can you walk me through how the situation is handled?

S03: Well I don't do a lot of Phase 1 trials [any more right] no [did you ever do any] no, A will tell you I'm a Phase 3 guy. [okay] But we're, but I have done Phase 1 trials and we're about to start a Phase 1/2 trial in the same situation. So, if the patient um, had an adverse event, it depends whether you mean adverse event or serious adverse event, there's a big difference. [yes] Unfortunately, many of the cancer patients because of the nature of their disease, underlying disease um, have lots of adverse events, you know, nausea, vomiting, pain, blah, blah, blah, blah that are not necessarily related to the study medication and most likely are not related to their study medication. Similarly, many of the hospitalizations in these patients, which is by definition an SAE, um, are not drug related. So I think you need to be more specific with your question [okay] because if a patient has an AE um, for example they have a little bit of nausea, that's a grade 1 AE, I don't give a shit, excuse the expression A, explicative. **(No**

concern for minor reactions) I mean so what, they all have toxicity, I don't see that as a, as a, as a, I wouldn't bother with that, it's a mild um, situation unlikely related to the drug. So I wouldn't, you have to be more specific in your question. [okay]Are, are you, you know, if, if there is a situation where there's a more severe um, adverse event, like a 3 or 4 toxicity.

M: Alright then lets talk more specifically about a serious adverse event. [yeah, an SAE]

S03: So what I do, well I don't do much, the clinical trial nurse does everything. **(Clinical trials nurse is more actively engage in causality attribution over medical oncologist)** But basically the, what's supposed to happen is that it's supposed to be documented first on the report form and also by the nurse on a SAE form. Usually most sponsors have their own type of SAE form. And then um, um, then that's forwarded onto the sponsor. I think that where the difficulty lies is attributing the SAE to study medication or not and that, that, what, what, what we, what I try to do in many of the studies that we, my group coordinates is that we actually try to put in the protocol that any, any, um, SAE or such that is clearly attributed to the tumor or the underlying cancer is not, not necessary to report as an SAE or etc, etc. [yeah] **(Doesn't bother reporting AEs attributable to the disease)** The FDA doesn't always buy that, Health Protection Branch, TPD will, but the FDA hasn't when we've tried it a couple of times. So I mean what you do, you fill out the forms, I don't fill them out, the nurse fills them out and you sign them, investigator and it goes off to um the sponsor and then the sponsor decides. I think where the difficulty is attributing um, whether it's related to the drug. And um, I mean sometimes it's clearly not related, like patient commits suicide [right] patient gets hit by a car, it's clearly not related [right]. Or it's clearly you know, a complication of an operation, you know, it's not drug related. Um, sometimes it's grey, you know, maybe could be and that's the difficulty. And, and ah, um, what really annoys me is when investigators at other sites don't pay attention to this and let's say there's an SAE they attribute it to you know, very

likely study drug. And let's say, and they also tick off unexpected, you know, which is if an SAE is related and unexpected that's reportable to regulatory authorities. And then when you look at the patient, and it's happened at another site, across the world in another study, another trial that sponsor is doing and then you get and you're, you get this piece of paper and it says you're supposed to give it to your REB and you read it, you say, my goodness, this has nothing to do with the study medication, it's due to X, Y or Z. **(Annoying when different sites are working on the same protocol drug, differing opinions)** But you are obliged to send it to your REB with a covering note saying what your own opinion is. [right] **(Opinionated process)** So an investigator has to pay particular attention to the um, the relevance of the reaction or the toxicity to the drug. You gave me two reasons at the beginning but the, one patient safety and the second I forget what you said, but the third reason is, if it's done incorrectly, it's a pain in the ass for all the trial nurses and all the invest, all the trial doctors all over the world because it takes time to sort out. **(Misattributing can have serious, global consequences)** [yeah] So there's a long-winded ah, but that's what I do.

M: So when you're trying to assign causality what are the resources that you refer to?

S03: My head. Well you can look first at the investigators brochure, you, that, that's what you're supposed to look at. You, you look at also what you know about the underlying disease, ah, discuss it with clinical trial nurses, you discuss it with the local PI. And if you're really not sure you can go to the PI for the whole study. **(Uses personal experience and knowledge to make decisions)**

M: Any other resources that you use?

S03: Um, the web, if you think, you are saying Phase 1 so there's not going to be anything on the web for Phase 1 study. But if it's, if it's Phase 3, Phase 2 or 3 there might be stuff if you do a literature search?

M: Are there any tools that you use to help you in assigning causality such as flow charts or algorithms or you know?

S03: Just my clinical judgment.

M: What sort of

S03: And you can, A as you know, I'm always right. [laughter]

M: And what general guidelines do you follow then when you're assigning causality?

S03: Well I look at the, well first I look at the protocol, and I, and I look at what the protocol specifies for in terms of causality. Often, each company or each sponsor may have slightly different wording for, I've noticed that. So whether its related or not related, the various gradations in-between may be slightly different wordings in English. So you have to be careful, so I read the protocol, I look at what the protocol says, that's my starting point. **(Cautious Protocol)**

M: Any other sort of general guidelines to do with causality, rules of thumb that you use?

S03: My common sense [yeah].

M: What do you consider to be the most important factor when you're assigning causality?

S03: I don't know what you mean.

M: So presumably there's many things that come into play when you're assigning causality maybe the patient's, you said their underlying disease, maybe what you know about the drug.

S03: Which is the most important? Do I have to give you the most important?

M: Well if you don't think there's any one that's most important then.

S03: I think it's a constellation, it's an assimilation of timing, severity, in, in other words, you know, by severity I mean, is it, is it, have I never seen this before like the rarity. I don't know what the right word in English is [yeah, yeah, yeah] rarity I guess, severity, timing, um, is it, is it something that can be explained by something else. Those are the types, some types of things that I look at.

(Seeking explanation for cause and effect)

M: Now I would just like to ask you now to consider this scenario. [scenario, sure] Let's say you're treating a 65-year-old female patient with a confirmed diagnosis of metastatic breast cancer. [yes] She's in a Phase 1 clinical trial with a new investigational drug and she experiences a pulmonary embolism. How would you assign causality to the drug if you knew that there was a 75% chance that the adverse event was due to the study drug and a 25% chance that it was due other factors, such as adjuvant treatment, disease progression, concomitant illness, concomitant meds and the grades were certain, probable, possible or unlikely.

S03: Okay, so first of all the patient has metastatic breast cancer and she's on a Phase 1 study. She presumably because she's on a Phase 1 study she's probably had other therapies for metastatic disease so she's pretty, she's got advanced disease. People with metastatic breast cancer um, um, metastatic cancer are prone to PE. So, you, you, you know she could have gotten the PE and it had nothing to do with the drug. On the other hand there are some Phase 1 drugs that are anti-VEGF, anti-angiogenic that appear to be associated with,

with pulmonary embolism. So I think I would use your third one down which I think was possible [probable] no, no, no [there was certain, probably, possible or unlikely] possible.

M: Okay, even though there was a 75% chance that it was due to the study drug and 25% chance it was due to other factors.

S03: Well I don't know how you, you can decide that unless you have other, um, other information from other Phase 1 studies [yeah], is that what you mean by the probability? [yeah] Like if you said to me

M: Just based on, it's really an unlikely scenario really, because you never know what those probabilities are [well] but we're just trying to get a sense of what you would attribute to

S03: But if you said to me this Phase 1 drug was an anti-angiogenic agent or an anti-VEGF, I would, and maybe that's what you mean by 75 probability % you know. It would be more helpful for me to answer the question if I knew what the drug was targeting because anti-VEGF or anti-angiogenic drugs appear to be associated with thrombosis. So if you told me that was the Phase 1 drug then I would say very possibly. But it's, it's very difficult without, maybe that's what you're getting at by saying it's a 75% probability because that's the only, that's you know...

M: We didn't have any drug in particular in mind for this, it's just trying to get a sense of you know, what your thresholds are for calling it possible, versus probable versus unlikely.

S03: But where's the probabilities come in, that's what I'm not understanding.

M: I know, it's hard, it would be nice if we knew what those probabilities were all the time right but we don't necessarily.

S03: Well I'm going to stick with what I did.

M: That's fine, I'm not asking you to change your answer at all. [right, right, right] But let's say there was a 50% chance that it was due to the study drug and a 50% chance it was due to all those other factors would that change your?

S03: No, no.

M: You would still say possible. [mmm hmm]

M: And what if there was a 20% chance that it was due to the study drug and an 80% chance...

S03: I still say possible. [still say possible]

M: So what would it take for you to say it was probably related to the study drug or was unlikely related to the study drug?

S03: Well again, if you told me what it was [this is just hypothetical] yeah, well I think on the bottom side probably about 5% from possible to not. And on the top side you gave me 75% to start at the top, [mmm hmm] probably about 80% [for it to be probable] yeah, yeah.

M: And so given the choice would you prefer to grade causality as certain, probable, possible or unlikely or as a yes related to the study drug or no not related to the study drug?

S03: No, no, no, it has to be graded [you need a scale] you need a scale. Because then you're going to, by just having it categorical to yes or no you're going to end up um, okay well wait a minute by yes and no do you mean, but you have to, like yes means like yes, definite. Is that what you mean by yes?

M: Yes related to the study drug or no not related to the study drug.

S03: It's never like that [it's never] oh you know out of every 100, it's a, it's a slam dunk, I think that's not a good that I, I mean it's so rarely a slam dunk that's, I, I, you need a gradation. **(Certainty is rare)**

M: What would you say are some of the problems or challenges with assigning causality? You mentioned just the complexity of these patients [yeah] with advanced disease.

S03: Reproducibility so that, by reproducibility I mean not only interobserver, you know different people rating causality but also the same people, am I consistent over time, probably not, but it's both inter and intra so that those are problems. **(Feels they are inconsistent)** Um, the whole, I mean probably the whole thing is overkill, that we end up having to grade causality probably is irrelevant for over 90% of all the AE's. [why do you think?] Because any, as I said to you earlier, many of the AE's, everybody who has cancer on treatment is fatigued. So do you fill out a, do you fill out, do you bother doing an AE for mild fatigue? There are lots of people with breast, bone, always have pain but they live with it. So many of the AE's, I get such a push back from the clinical trial nurses when, when, on this subject of mild AE's, many patients have and they have them all the time. Do they have, they're tough you know, why bother filling them out, so the whole process has gotten out of hand. **(Feel reporting mild AEs is a nuisance)**

M: But if it's just a matter of recording them in the case record form.

S03: Well if you have, ah, ah following the patients with this and it takes how many minutes or hours to do it, it's very costly [it adds up] it's very labour intensive. **(Feels reporting minor AEs wastes time)**

M: Well what about if a patient has a number of low-grade toxicities which overall is really hard on them?

S03: Right, but they're probably not, first of all they're probably not related to the study medication. [okay] **(Feels minor reactions are not hard on patients)** They're probably related to the underlying disease and yet you're not 100% sure that you can't attribute in part, a little tiny bit and you're sort of chasing your tail. Because they certainly could be explained by the disease of interest, um, not by the drug but if the product monograph says nausea how do you know if the nausea is due to the cancer or you know what I mean? [mmm hmm] so it's gotten to the point now in my own view that the whole bureaucracy of this is unwieldy and it's getting worse not better. **(Feels clinical trials are failing in terms of causality attribution)**[yeah] And ah, it's actually going to kill, it's going to, it's going to kill clinical research, the whole administrative bureaucracy that's involved. And the ICH/GCP guidelines which this is part of is, is, ah, is making it very, very difficult to do this sort of research and it's unfortunate because you know, we need to study new drugs, we need to, yeah.

M: What are your concerns about how clinicians currently assign causality? You mentioned the concern with the REB's receiving reports.

S03: Yeah, you know, my concern is sometimes not enough attention is paid or they don't understand sometimes what the implications are so they don't give it enough time, they don't understand it. This whole problem of inter, people, different people don't agree on the categorization so that something I would call unlikely, they might call likely. And the whole again gets these, if something is

reported as serious related and unexpected it sets off a whole chain of reactions around the world.

M: What external pressures from third parties have you felt when assigning causality?

S03: None.

M: From your perspective, what would make assigning causality easier?

S03: No, because these patients are often so sick. What we've done as I said to you, but it's not assigning, well it is, we've tried to, like we get the protocols, we've tried to get statements put into the protocols saying, if, I'll show you. I'll see if I've got some stuff here, what have I got. [the safety section] Okay, so here's what we put in one of our studies that I coordinate. In terms of the SAE definition, hospitalizations exceptions, criteria for hospitalizations not related, reported as SAE's, planned as per protocol medical surgical procedure okay. [right, obviously yeah] Planned chemotherapy, routine health assessment, you know dah, dah, dah, like colonoscopy. Medical surgical admission for purpose other than remedying ill, ill health state, in other words they were planned ahead of time [plans] admission to account for other health circumstances that has no bearing on health status. So I mean, we've actually with other people gotten more extreme um, in terms of um, had language sort of saying if it was an admission for the underlying cancer it's not an SAE you know, that sort of stuff. So those, you can, you can put exceptions in so that if people think about them ahead of time, it, it does cut down, a little bit on the bureaucracy [yeah the administrative burden] right, so we've tried that. Um, for our radiation trials, where, where, where um, radiation trials sort of haven't yet got on the radar screen of the regulatory agencies because it's not investigational drugs. Um, we've really um, we do AE's and SAE's but very modified, only related to the radiation therapy, only severe grade 3 and 4 [right] much more practical approach. So that's made,

I mean it's almost from the experience we've had with drugs and what's bad about the AE/SAE reporting of drugs we've done some nice templates for the radiation trials which are really much more practical. You know, really zeroing in on toxicity related to radiation, organ system toxicity related to radiation and that sort of stuff [right] very practical. But that's not a tool for grading or categorizing AE's and SAE's.

M: No but that's definitely something that's making it easier. [yes, definitely yeah]

M: What I'd like to ask you now is to do a little exercise for me if you don't mind. So I'd like you to read these following questions cross out any that you feel are not related to or are not relevant to the Phase 1 oncology setting. This was a tool that was developed by a fellow named Naranjo, he developed an algorithm to help clinicians assign causality.

S03: They're all good.

M: Okay, great, then now would you be able to rank them in order of importance in terms of, [laughter], I know it's quite an exercise, 10 would be most important and 1 would be least important. [okay] Great, so I see that you've crossed out number 6 and why did you decide to cross that one out? [well because] Did the reaction reappear when a placebo was given?

S03: I think it's a stupid thing, stupid because I can't, I don't think it's ethical in a Phase 1 trial that if you have an adverse reaction to the drug to try to trick. I mean basically what you are saying with the placebo is that it's a psychosomatic type thing. You can give the placebo and the reaction still comes out. I'm, I'm not sure in a Phase 1 study it's that important to ascertain that sort of thing by rechallenging the patient with a placebo. There's all sorts of ethics involved with that so I had a little difficulty thinking it was particularly helpful.

M: And that's not usually done is it? [yeah] You ranked um, was the adverse event confirmed by any objective evidence as 3 which is fairly low. What did you understand to be, objective evidence [well] what was your impression of that?

S03: Let's say, because I think many of the, I mean there are, when I think of adverse reactions so you're thinking of the, I guess why I had difficulty with that is some adverse reactions are very lab dependant or diagnostic dependant. Say let's say a drug causes lung toxicity, well you'd like to see it on a chest x-ray, you can't just say because someone is short of breath. On the other hand, if a patient develops severe anaphylactic that's a, you don't need any tests, that's a clinical history and physical, you know. So I wouldn't, just because, if I had, if a patient experienced what I thought was a you know, a, a severe adverse reaction and I didn't have a lab, a blood test or chest x-ray to back it up, you know. They're admitted, basically patients um, you know, drops their blood pressure in their boots and is admitted to the hospital with shock with no blood pressure, that's a clinical diagnosis. I mean, I mean I don't really interpret a history and physical as objective evidence. I mean a physical exam is objective so I don't think it's a good question but if said. [okay]

M: Was the reaction more severe when the dose was increased or less severe when the dose was decreased. You ranked that as 4 [mmm hmm] that's not as important as other things.

S03: Because if you suspect, again, if you suspect it's a bad drug reaction you're going to stop the drug. And again it's a little bit like the placebo thing, you're not going to sort of for a Phase 1 study try to demonstrate a dose response relationship. So that, that, I didn't dismiss this totally outright, but I think it's really the issue in a Phase, for a severe drug reaction does, does it come out on rechallenge that's the, that's important. Not by fooling around with the dose, big ethic issues with that.

M: And then whether it was detected in the blood in concentrations known to be toxic, you rated that quite low too, what was your reasoning for that?

S03: Generally, um, in many of the Phase 1 studies they collect blood for pharmacokinetic and pharmacodynamics. Those are frozen, batched and done six months later, well the patient is dead by then **(little emotional attachment to patient)** [yeah you don't] so they're useless, it's useless to, it's not very important.

M: You just don't have that information at the time [yeah] when you're assigning [yeah] causality. [yeah, yeah]

M: Great, that's and then were there any questions that you thought should be here but just weren't on this list?

S01: I really hadn't thought about it. [okay, just let me know if you think of any]

M: And then lastly I would just like to ask you a little bit about your experience as a clinical trial researcher and I know this could take some time. So, you specialize in breast cancer right.

S03: Yes.

M: Any other special areas you specialize in?

S03: Thrombosis.

M: When did you get your MD?

S03: 1976.

M: And your oncology license?

S03: I don't know, um, I started, I started, 1981. [81]

M: And I see that you did the Masters in ClinEpi here at Mac, when did you do that?

S03: 1982.

M: And is there any other education that you have that I should know about?

S03: No.

M: Any other certifications, clinical trials that you've done?

S03: A lot of clinical trials.

M: And what year did you become involved as a clinical trials researcher?

S03: 1982. [1982]

M: What percentage of your work time would you say is devoted to clinical trials?

S03: [27:34 – skipped – did not hear answer 70%]

M: Of that what percentage of the 70% is related to, is spent doing Phase1/2 trials.

S03: 0%.

M: So it's virtually all Phase 3 [yeah].

S03: Oh wait a minute, wait a minute. See the problem is I coordinate a trials group, so some of the work we do, actually we've got a couple of Phase 1 studies. Well I better fix that up there [okay] probably, it's probably 10% Phase 1 [okay, 10 and 60] 60 yeah.

M: And you've been a local PI obviously before yes?

M: And can you tell me about any training that you've received specifically with respect to assigning causality?

S03: I think the, you know, every time you, you write a protocol you come up into the administrative section and each sponsor does it differently. So just by reading and writing the protocols you learn about it. Um, second, for example, as the local PI for a trial that we're about to open, this one here, [oh yeah] I wasn't, I had to go onto the sponsors website and do um, a course, ah, ah and questions related to ICH guidelines and, and one of those, part of it was on AE's and all that crap. It was very good actually, it was excellent. [which one, who was the sponsor for that one] BMS [BMS] yeah, that was..[so there were questions and a little exam] yeah, yeah, yeah. So I flunked them first and then I did the whole course and I passed after, it was good, it was good.

M: What additional education about assigning causality do you think should be made available to clinicians?

S03: I think that sort of thing. [that sort of thing] I also had to, you know, the third thing I did was, all of us who hold, what the hell is it called, you have an investigator number with the US [NCI] NCI and to um, initially get that number you have to do an online course related to regulatory issues and all that stuff. It was very similar to the BMS thing, so I, I had to do that a number of years ago to get the NC to get the regu, the investigator number with the NCI. [and then that

was their, was there anything about causality?] There was, there was, this is an AE, this is an SAE, these are the criteria to grade them, that sort of stuff. [yeah, nothing specifically about how] how, no [how to assign] yeah. [maybe that could be incorporated] I think a little, a little, I know A is crazy about electronic stuff, a little CD or a little thing, a web-based thing where you went into and ah, you know, with Microsoft multimedia or something like that. You could do a really nice little [tool] tool with some examples and a test and all that sort of stuff. It could be kind of, I think that would be very useful. [great]

M: Is there anyone else you recommend I contact with respect to, we're also speaking to clinical trials nurses so if there's anyone you recommend.

S01: I don't know who you're talking to but um [I've pretty much talked to all the investigators here at the JCC] okay but have you done any on the radiation side.

M: Well we purposely excluded the radiation oncologists. If not that's okay.

S01: Yeah, I don't think, yeah you've done the trials nurses I think.

M: Yeah, we've got a sample of them. Okay great, well I really appreciate the time you spent with me today because I know I've gone over and I know you're very busy, but yeah, thank you.

Subject 04

M: Okay, so I'll just ask the question again. [sure] Let's say one of your Phase 1 clinical trial patients has just reported experiencing an adverse event. Can you please walk me through that situation. [okay]

S04: So do you want to know from a practical point of view how it's handled [um] or do you want to know from a [yeah] causality point of view how we might assign. [both would be great] Both, so I guess practically ah, it will depend on the nature of the adverse event, if it's something that seems fairly mild often we'll for

all intensive purposes deal with, deal with it over the phone. Um, if it's something that needs assessment in the clinic then we'll kind of bring them in for a face-to-face assessment. And some of the decisions sometimes rest with where they are in the treatment protocol. If they're already on active therapy then we will see them physically face-to-face. If they're, they're during a week where they're off therapy or in some sort of a follow-up phase then we'll, probably we'll deal with it over the phone. So that's kind of practically how we deal with it. From a causality point of view, I mean there's more stress if the adverse event is of a more serious magnitude in terms of determining how related it is to the trial medication. And I think a lot, a lot of that has to do with you know, how do you make the decision **(the decision making process is very important)**, it's difficult sometimes, sometimes it's pretty straight forward that they're experiencing an adverse event that is known to occur with the study medication. Sometimes though for a lot of these newer drugs we don't know what the side effect profile is necessarily [right] and so you take that into account. Sometimes you have to know their underlying co morbidities, whether or not there is some other underlying illness that the patient has that could be creating the side effect. I think between those two you kind of try and figure out is it related to the drug or not. I, for ones that are clear-cut, known to be associated with the drug from other experience I would tend to rate those as being more causal if it's fairly straightforward. **(Errs on the side of caution)** I think if it's not straightforward, I kind of, I put the causality as somewhere in between possible or [2.27 not sure if skipped]. For one's there is clearly an explanation, a patient's co-morbidity disease or some other co-existing illness then I'll clearly put them as unlikely. I think the ones that are, I think the ones that are easier to score are the ones that are clearly not related to the drug because of those reasons or the ones that are clearly related to the drug based on one's own experience and the literature on that agent. The ones that are difficult are the ones that are in between, that's, it's difficult in that sense.

M: Can you give me an example of one that would sort of be in between?

S04: We've had a lot of experience recently doing Velcade® studies bortezomib which is a proteasome inhibitor. It typically causes fatigue and peripheral neuropathy and low blood counts and change the bowel habits usually causes either constipation or diarrhea. Those patients are challenging because some of them already have neuropathy left over from their previous therapy, it's often mild but it's ah. So if that neuropathy clearly gets worse during the study then I would ascribe it to the drug itself. Some of them have diabetes too or they've had shingles and it's really hard to know whether, if their neuropathy is getting worse. I mean it may just be their underlying disease rather than the drug itself. For those situations I would tend to assign causality to the drug less ah, directly. So that, that was a common theme in the Velcade studies. And the other thing in the Velcade studies was you know, changes in bowel habits and that because these patients are on narcotics, so they're already taking medication known to cause constipation. They're on Velcade as well which can cause constipation, also longstanding left over from their previous treatments. So it's really hard unless the grade of bowel disruption is very high or it's obvious that things have gotten a lot worse and nothing else has changed then I'll say it's probably the drug. But in the setting of day-to-day variations say in someone's bowel habits it's really hard to know I'll tend to be less causal in terms of the connected side effect.

M: What are the resources that you refer to?

S04: Actually not any that I know of. I mean for drugs that we have personal experience with that are just being used in a new way or in a new dose schedule or a new disease then those are a little bit easier because you do have some experience and there's a bit of literature already about the potential adverse effects. So I think, those ones are okay because you're basing it a bit on personal experience [yeah] and a little bit on what's published. For the really new drugs [yeah, say in a Phase 1 study] in a Phase 1 nobody has any experience with then, you are kind of stuck, you're going on what's in the files, monograph, the study design in terms of anticipated risks and side effects basically. [yeah, they're

outlined in the IB] Yeah exactly. But apart from that I don't know of any other way of getting more information than what's there for a drug that's really early on in Phase 1. At times you know, we'll do Phase 1 testing of combinations of drugs that are more known and I think in that situation too sometimes it can be a little bit tricky trying to figure out what's happening in the combination, what side effects, maybe is there one drug that's more responsible than another. [right] Those are definitely, other than the brochure, really there's nothing I know of.

M: What sort of tools do you use to help you assign?

S04: Tools in terms of um,

M: Decision trees, Algorithms, are there any sort of general guidelines that you follow, you mentioned when you are more likely to assign probable and possible.

S04: I can't say that there any actual guidelines that I know of or that I specifically follow. So it's more like each case, hopefully, you know, the fear is that you're not consistent I guess, that you know, you're scoring a patient differently, that's, that's the fear. **(Afraid of inconsistency)** So I think I don't use specific guidelines, I try and, I try to be mindful to score the causality in a similar way. Because some of the side effects keep popping up in different patients, for the Velcade example, constipation and fatigue and neuropathy they're like recurring events that the nurses have scored. So I try to be consistent in terms of you know well, did they have neuropathy when they started or what medications have they been on, where are they in their treatment. I try and use all that information to assign causality, I don't know, I don't know, I don't use anything directly any other way. **(No tool to ensure consistency)**

M: Where they are in their treatment, what do you, how is that important?

S04: Like if the adverse event came up and it was after the treatment or depending on the chemo schedule, was it, was it on their week off or [trying to get at the timing like how soon after] yeah [the drug was administered?] yeah. Kind of like nausea, vomiting for example in their treatment week, that would be you know, more likely to be drug related. Rather than saying nausea, vomiting that occurred in their week off [right] in their third week of a three-week regimen. **(Use timing to cope with uncertainty)**

M: What do you consider of those to be the most important factor of all those things that you mentioned?

S04: In assigning causality? [mmm hmm] Oh I think timing is, I think timing would have to be the most important thing. [why?] Well, I guess it kind of makes intuitive sense, that if a drug is given on day one and there's a certain schedule to it which is based on some pharmacokinetic principals. You know that drug might be, out of the circulation by day 7 so you might expect any adverse events in the first few days after the administration. **(places strong importance of timing of event to cope with uncertainty)** Where it gets tricky though is if it's given on day 1 could cause some of neutropenia like fevers or that can happen later on as well that are related to the drug [link back a few steps] link back yeah. But I think timing is important and I think, well that's probably the most important. And I think the magnitude of the event probably has something to do with it. Somebody that has a little bit of nausea that grumbles up and down are obvious if they had, you know, they get the drug on day 1 and on day 2 or 3 they have [when you say magnitude you mean severity] the grade, the severity yeah. [okay] I think timing will probably be the number one.

M: What I would just like to ask you to consider this scenario. So let's say you're treating a 65-year-old female breast cancer patient and she's been diagnosed with metastatic breast cancer. [okay] She's in a Phase 1 clinical trial with a new investigational drug when she experiences a pulmonary embolism. [okay] And

you don't know anything about the study drug [right, okay]. How would you assign causality to the study drug if there was a 75% chance that the adverse event was due to the study drug and a 25% chance that it was due other factors

S04: 75 versus 25% how would I assign causality?

M: Yeah, if the grades were certain, probable, possible or unlikely.

S04: I would say probable for that one [okay] that's the second one from the top. [yes] I would have to say probable.

M: Let's say you knew there was a 50% chance that it was due to the study drug and a 50% chance it was due to...

S04: Same grade, I would go one level below probable which would be what possible [possible] yeah.

M: And what if there was a 20% chance the adverse event was due to the study drug and an 80% chance it was due to...

S04: I would still go with possible [yeah] part of it is [can you elaborate there] yeah, part of it is, I mean it seems logical to just go down one more step and say, I don't know, what's below possible [unlikely] unlikely. And say well of the issue is where, you know, where to draw the cutoff in the numbers, is 20% unlikely, is it 10%, is it 18%, 25 and I guess. So that's one issue, and the other issue that might, that might trump the number a little bit is the, is the adverse event itself. So like pulmonary embolism is, could be life threatening. [yeah] So, if, if a certain drug was associated with a side effect that could be life threatening I would be inclined even at lower rates of probability to assign it as being more likely than just based on the number itself. **(err on the side of caution with serious adverse events by attributing it to the drug)** So with the pulmonary embolism,

so I might go down to 10% even, to be kind of [that would sort of be your cut off rate] yeah. In terms of to just make sure there was a potential warning there. [10% or less would be unlikely for you] Right, if it was like nausea and vomiting say, I'd be, I'd probably not be as likely to assign causality and that's to do with the severity of the side effect.

M: And given the choice would you prefer to grade causality as certain, probable, possible and unlikely or as a yes related to the study drug or no not related to the study drug?

S04: Um, I do like the grading because it gives you a little bit of leeway and you could argue about what each term means, but I do like the multi-level grading it gives you a bit more choice.

M: What's not good about the yes or the no, is there any...

S04: Well the yes is, I mean, worthwhile knowing whether the drug is highly likely to cause an adverse event, or possibly or unlikely rather than just yes or no. Like I find that information useful, whether it's kind of possible or probable or likely.

M: So you think it would be that, that, having that gradation is more useful to your colleagues also probably [yeah] they would find it more useful. [I would say so]

S04: Because we don't, we all think in statistics anyway, we all think, even in day-to-day care of patients there's the mindset of different levels of, that the patient, given a certain treatment for disease x that their probability of survival, it's not just 100% or 0, there's always some probabilities of, so like we, what I'm trying to say is we talk in probabilities all the time. [yeah] So rather than just 0, like on or off. **(uses a statistical mind frame)**

M: What would you say are some of the problems or challenges with assigning causality?

S03: Oh, I think um, the fundamental problem is really, for a new agent that's being tested is hard to get around, obviously if, if there are disastrous side effects then I think it would be easy to assign causality. But in the absence of that I think it's around the lack of experience is difficult. [with the new drug] Right. Often you know, part of the dilemma is when you're doing Phase 1 or Phase 2 studies, particularly Phase 1 I guess, there could be multiple Phase 1 studies done for a given agent. Unless you are in the loop with people and talk about things offline, there's really nothing printed to go on to say that the side effect in this given patient has never been reported before. **(lack of info on protocol drug, use communication to cope)** It could be that other people have seen it but it's not something that's been published in any formal way. So I think part of the challenge is getting people who do Phase 1 studies to really communicate with one, with each other to try and get a sense of some of the adverse effect profile of some of these newer agents if possible. But you know, when you talk casually to colleagues at other centers who are working on similar drugs you might you know, review cases with them. And say you know, have you ever seen this with this drug, it's kind of an informal way of, not really assigning causality. Because I mean you're [?14:07] it on that given case but it gives you a sense of whether other people are seeing similar problems.

M: What are your concerns about how clinicians currently assign causality?

S04: There's, there's two concerns, I think one concern is you know, over assigning causality. Because patients are, they can get sick, morbidities, multiple medications, actually a lot of reasons and it sometimes it's easier to blame it on the drug. But I think my fear is that if you, if you do that liberally you'd be, not discrediting the drug but you're not um, it could lead to dose reductions, could

eventually work their way into an ineffective treatment schedule for that.

(Apprehensive to make causality attribution) If you saw a whole bunch of side effects that you thought were you know not really related to the drug and that led to that drug being less developed in a certain disease. Maybe you're doing a disservice to that patient population, so that's one, that's one concern I have.

Perhaps over-assigning causality just because of the complications of some of the patients on the program is my biggest concern. And the other concern is, the other, completely opposite really is the not assigning causality and then drugs are allowed to develop. And then it's only when you start getting into Phase 2, Phase 3 studies that you really, adverse events really show themselves. And you're thinking well why wasn't this picked up in the Phase 1 or 2 studies? [yeah] So I think you can go either way, you can make errors on either way, one way you might kill a drug that might be successful and on the other way you might let a drug develop not carefully enough. **(error- strong term)**

M: What external influences or pressures from third parties have you felt when assigning causality?

S04: Pressures from third parties, none, I don't think so, I haven't you know, I haven't really personally felt the pressure to assign or not assign causality. I mean the biggest stress, not that I've had any stress about it, but the biggest issue is assigning causality that could result in a Phase 2 program going to a lower dose or something like that or you know a ineffective dose for a given cohort of patients is a concern, whether you're doing the, you made the call because that's often a critical step in a clinical trial. But I don't feel particularly stressed about it, I think you just call it as it is and then if it means the dose gets reduced for the next cohort or they stay the same, I mean so be it. I think Phase 1 studies are carefully crafted, to look at significant adverse subjects for example. So other than that I don't think there's any... **(little concern for minor AEs)**

M: From your perspective, what would make assigning causality easier?

S04: Um, I think if there was some sort of road map to use it might be, I don't know how that would look. I mean you're looking at an interplay of you know, patient factors, specifics about the clinical trial, I don't know how you would build that into some tool that clinicians could use. **(designing a tool would be difficult)** If there was something to use to go on to say well this case, given what I know about the patient and their comorbid diseases and the medications they're taking, what I know already about this drug, then I should score this event as a likely, or a possible or a probable. So having a bit of, guidance about those specific terms because I suspect people interpret them differently. **(need for more guidance)**

M: With this roadmap, how could we be assured that you would use it, you know best fit into your day-to-day?

S04: Well anything else, like day-to-day I think, I mean you're talking about more causality in a clinical trial setting. [yeah] So we're, we're already pretty used to using other tools, sort of you know, other scales and measuring for hematological toxicities for example using gradings. So I'm used to using scales in clinical trial patients, so I think having, having something printed or on paper that one could refer to wouldn't be a burden in that situation. And I think where it becomes much more of a loser is assigning causality casually say in the clinic on patients receiving medications, like not on trial. Where it's much more, there's probably the, the margins in that situation are probably much wider in terms of what people will call because they're not under that clinical trial scrutiny, they don't have to make the causality so. **(reporting isn't taken as seriously outside the trial)** [how's that different] Well it's different in the sense that well you know, like say you have a drug that's been used for years, you kind of know the side effect profile and you think so the patient has an adverse event and you think, well it's probably it, it's probably related to the drug but if it's mild he'll continue on. I

mean it's, you don't, you don't generally get to worried about, now if it's severe you know, you'll deal with that. **(little concern for mild AEs)** But for, you're not going to worry too much about whether it's, for mild events, whether it's going to be highly likely or probable or possible or unlikely. You do what you need to do for that patient's treatment. [right]

M: In a clinical trial, even the mildest adverse events are, you have to assign a causality.

S04: You have to assign a causality, you need to know when it started, when it stopped, there's a bit more rigor. Whereas in the clinic I think things are a little bit more loser, maybe from a more bookkeeping point of view, that way they are a little different.

M: What I'd like to do now is ask you to do a little exercise for me. [sure] So I was just wondering if you could read those questions and cross out any that you feel are not relevant to the Phase 1 oncology setting.

S04: Just cross them out if I feel that they're not relevant? [yeah, cross any out that you don't feel are relevant] On Phase 1 I guess, I mean there's not often placebo in a Phase 1 study. I'm going to cross that one out because I can't imagine a situation where, where the treatment is placebo, I can't imagine. And the drug detected in the blood in concentrations known to be toxic. I don't know about number 8, the reaction being more severe depending on the dose, I mean it's hard to know. Probably that's going to depend on whether there's any knowledge about a dose effect of the drug. I don't know, I might put a line through that one. I think the other ones are relevant.

M: And then, of those remaining ones could you just rank them now in order of importance [okay] so 1 being least important [I see okay] .

S04: 1 is least and 10 is most important right [yeah].

M: So just to give me a sense of which ones you think.

S04: Previous conclusive reports probably should be on the list first so I might have to cross, rearrange them a little. [sure, that's okay, take your time] Okay [all done] rank the other two I guess, okay.

M: Excellent. And so number 7 you ranked the lowest, was the drug detected in the blood [blood levels] why was that?

S04: Ah, I don't know, I think, many drugs, I think there's, there's a disconnect often between what you might be able to measure in the blood and what the side effect might be and I'm not sure that that's been worked out. I'm sure there's drugs that, that holds very true levels and, I'm sure, my, my impression is for many drugs it's we don't really know toxicity and blood levels that they go very well together. [yeah]

M: Great, that's wonderful, can I keep that [yea] thanks. Then were there any other questions on here or questions that you thought should be on here that weren't included?

S04: No actually it was a good list.

M: Any thing that came to mind. It was actually a tool developed by a researcher named Naranjo and ah, he made this to try and help investigators when they're assigning causality.

S04: It's actually, I mean it's a comprehensive list. I mean you could see for some of the drugs that we use, you could easily run through this list and fairly quickly come up with yes and no's for each of these. Placebo thing might not be

relevant, blood concentrations may not be known so that might be, so some of these could be quickly irrelevant, I mean just speed right through it. So that's, it's an interesting list, I have to admit I've never seen this before.

M: Now the last thing I would like to ask you a little bit about your experience as a clinical trials researcher. [yeah] so in which cancers do you specialize?

S04: Ah, all the blood cancers, so mostly lymphoma, myeloma.

M: What year did you get your MD?

S04: 93.

M: And what year did you get your medical oncology license?

S04: That would be hematology, so that would be in [sorry, hematology] 97.

M: And do you have a Masters or PhD at all in any?

S04: A Masters, Masters of, Masters in Science, yeah.

M: Okay, where did you do that?

S04: Here at Mac.

M: That was the ClinEpi program [yes] yeah. What year did you finish that?

S04: Oh it should say it back here, 2004 I think, when did they actually grant me the, 2004, hematology actually, what did I say. [you said 97] Actually 98, sorry yeah.

M: And what year did you become involved in clinical trials as a researcher?

S04: Um, I probably started here in 90, 2001 probably. [2001]

M: So overall, what percentage of your work time would you say is devoted to clinical trials?

S04: 10% say.

M: Yeah, and of that 10% what percentage is devoted to working on clinical, or Phase 1 or 2 trials.

S04: Phase 1 and 2 would be probably half of that.

M: and then the other half is on Phase 3 [Phase 3 yeah]. And have you ever been a local Principal Investigator for a trial? [yes]

M: And lastly I just want to ask you a little bit about the education you've received around assigning causality? So can you tell me about any training that you received specifically?

S04: Oh, very little, I mean I think um, a lot of the pharmaceutical sponsors that we did some studies with, had some training modules but not necessarily for causality mostly for adverse event reporting. Mostly, particularly for serious adverse events, mostly for clinical trials nurses to meet regulatory requirements, reporting quickly and that type of thing. But specifically causality in terms of the grading system, nothing really. [how to do it no?] No.

M: What additional education about assigning causality do you feel needs to be made available to clinicians if any?

S04: I don't know if there is any education, I don't know what even exists out there. [let's say there's nothing out there] If there's nothing out there? [yeah] then I think we, I think there has to be some way of teaching people perhaps how to score causality if it's on a 5 or 6 point scale. What's the best way of doing that I don't really know.

M: What would work best for you?

S04: I mean, me usually it's, an interactive session would probably work the best [like a face-to-face] face-to-face or working with something on a CD Rom, some sort of interactive program. Rather than a lecture or something like that, case-based, that type of thing [yes] that would probably be the best I think. [great]

M: Well I really appreciate all the time that you spent with me today. [no problem] I don't have any other questions and ah, the only other thing is I just wanted to know if there's anyone else you recommend I speak to, so we're talking to not only oncology [?].

S04: Yeah, either, well are you doing all this, this week.

M: Well over the next few months.

S04: Well, a few months, I mean, the two clinical trials nurses are TH and KH, they would both be, they are basically the two that run the vast, vast majority of the hematology trials, both of them would be good. [great]

Subject 05

M: Okay, so as you know, we're looking at how investigators assign causality [right] to adverse events that occur in clinical trials, specifically Phase 1 clinical trials. Even the most experienced clinicians find assigning causality to adverse events challenging and many groups expect prompt and sensible causality assessments. But assigning causality isn't straightforward, and if done poorly it

can have large implications for patient safety and also new drug development. So we're interested in developing a tool to help clinicians efficiently and reliably assign causality during Phase 1 oncology clinical trials. And we feel that by better understanding your needs as a clinician we can make our tool more relevant to you. Do you have any questions before [no] we begin, no okay. So first of all let's just say one of your Phase 1 clinical trial patient has just reported experiencing an adverse event. Can you please walk me through how the situation is handled?

S05: Yes, I guess the first thing is in terms of trying to sort out, I mean I think the issue is is it really related to the patient's underlying disease, the study medication or some other cause? Then based on what the temporal pattern is and what we know from the mechanism of the study drug you know, is it possible that, that. I mean clearly having to review a lot of these SAE's coming from everywhere, it's really a big mess in terms of whether it's a strong indication that the study drug is involved when clearly when you look at everything else. **(Very hard decision to make when there are confounding variables)** What I normally will try, the problem with Phase 1 drugs is, is that we don't necessarily know everything that we're going to expect in human beings so that, that the information that's in our expectations of toxicity don't always predict everything you're going to see. On one level I think you have to, to accurately reflect you know, whether it's study doing, study drug doing something that we think is in keeping with how you expect the drug to behave. On the other hand you have to be really able to capture kind of the unusual stuff that may not have anything to do with the way we think the drug works but still be able to capture that and do that in a way that you're not necessarily torpedoing a drug for things that may be you know, very tenuous in terms of their association. So that's kind of the, the way I try to approach when I'm, I'm seeing these kinds of things. **(copes with uncertainty by considering the known effects of the drug and paying attention to unique AEs)** So first of all you know, is there a temporal relationship, then assigning, depending on what we think the strength of that relationship is, definitely, probable, possible, unlikely.

M: What are the resources that you refer to when you're assigning causality?

S05: Well most importantly, when we see the patients we assess them so getting and the various lab parameters so, and the background information about the drug. So you have the investigate, the investigator brochure of the background and clinical data on the drug. **(patient history and history of the drug play a strong role)**

M: What tools do you use to help you?

S05: In terms of specific algorithms you have in mind or? [yeah, or decision trees]. I normally don't use anything particularly that formal. It's really just going through the information and the history and strength of the association.

M: What guidelines do you follow?

S05: We're usually using, we're usually given in terms of assigning the grade or are you asking something else?

M: Not necessarily, because I know there's the RECIST criteria.

S05: Yeah, the RECIST is more for assessing response [to tumors yeah] so for grading toxicity [right] we often use the NCIC criteria or, or the NCI or the WHO toxicity criteria are the ones we use most commonly just in terms of you know, whatever grade that is, whatever the cause. **(No consistent criteria to grade toxicities)**

M: But when you're actually assigning causality [yeah] like unlikely, probable, what guidelines do you use for doing that?

S05: Well it's really again just looking at, at the particular situation at hand and really putting together um, what we know about the agent and what the patient's reaction is and you know, what actually makes more sense. You know, I think the, the big issue always is in most cases is it due to underlying disease problems giving disease related symptoms or is the drug doing that. That to some extent you have to get a sense of you know, the history of the patient, their disease, the extent of their disease in terms of might that be causing. I'll give you an example [okay] so today we had a, had a one of our Phase 1 patients come in he's on a, on a ?? now, this was his fourth cycle. And all of a sudden his liver function tests were elevated, they had gone up dramatically, and they had been quite normal before so. This fellow has colorectal cancer which we know can metastasize to the liver, so the question for him was, do we think this is related to the study drug or related to something else? So how do you sort that out, so the first issue was from the history point of view, well he's had the study medication, he's had this for his previous three cycles and it hasn't changed so why should something suddenly change in the fourth cycle. So that didn't look like a strong possibility, is he on any other medications that might have caused this? Well, the other medication he's been on he's been on a long time so that seemed unlikely. Then the issue was well perhaps this is his disease progressing rather quickly and we looked at his CAT scan from two weeks ago and that turned out to be perfectly clear. So at the end of the day we're left with somebody who's got progressively abnormal liver function tests and what's the likelihood this is his study medication. My sense with the information we have is that it's unlikely, he's had it before, he's had the same dose three previous times. We have no other obvious explanation for it so can we say that it's absolute? Definitely not. I think it's unlikely but I think we have to leave the door open to say well maybe when patients are on this drug for more than three cycles there's there are cumulative effects on the liver. But you know, based on what we know, how, how strong is that, that association. So we're left in a situation where this guy has abnormal liver function tests and at the end of the day with all the things we've done, we

don't have anything we can say absolutely it's this. But based on what, what we know he's been through what his disease is, what the drug does, make some assumptions to say the likelihood that this is causality. It's clearly not a situation where you've got it black ... **(copes with uncertainty through process of elimination)**

M: In that case what did you assign?

S05: We're, it's going to be unlikely at this point in time. But obviously you know we'll have to re-evaluate that with time, it would be nice to have something that, that we can hang our hat on or eventually to say this is the cause.

M: What do you consider the most important factor then when assigning causality? In that example, it sounds to me that you didn't have any objective evidence of liver mets.

S05: It's got to be something other than disease, I think it depends on you know, what you know about the potential toxicity of the drug and guessing how could you definitively get an answer from this, well, he's stopped the drug now, does the toxicity start to reverse, ideally if you have the opportunity to rechallenge, things off again, obviously there's a question if somebody is quite ill from the toxicity it's probably not ethical. But in terms of the best way of actually trying to sort that out, that would be scientifically the cleanest way. Clearly if they're very ill and you're rechallenging then, that's obviously not ethical. But I think the most important strengths are if it occurred right or shortly after they started the study. **(Place a strong emphasis on timing of an event. There are clear ways to determine causality, but they are unethical)**

M: What I would like to do now is just ask you to consider a scenario. Let's say you're treating a 65-year-old female patient with a confirmed diagnosis of metastatic breast cancer. And she's in a Phase 1 clinical trial with a new

investigational drug and she experiences a pulmonary embolism. How would you assign causality to the drug if there was a 75% chance that the adverse event was related to the study drug and a 25% chance that it was due to other causes given the scale of certain, probable, possible or unlikely.

S05: Who made up that question, that's a tough one.....scale geez[laughter] that's a good, I mean that's the reality, that's exactly the kind of situation we face. And what was my scale? [certain, probable, possible or unlikely] Yeah, so I think, you know, I think really you have to be careful in terms of the extremes there I think because somebody with metastatic breast cancer certainly if they are on a new treatment has a possibility of having that kind of a problem. But I think given the high likelihood of the drug causing those kinds of problems I think you have to weigh it heavily on you know, very likely that it's caused by that so I would put probably there related to. And also include possibly underlying breast cancer. Again I think you need to get a sense of exactly when the patient started the study medication and when this happened. I think that would give you stronger evidence in terms of saying you know, if it started a short time after the patient went on this drug. **(Stresses emphasis on timing of an event)**

M: Now what if there was a 50% chance that it was due to the study drug?

S05: That's tough. Again, I think I would probably um, I would call it probably related to study medication. There you're getting, you're, you know it's hard to, to, how, how strongly are you going to implicate the study on the side of implicating the study drug just from these issues. Probably drug, possibly underlying disease. **(worried about implicated study drug)**

M: Now what if the, there was a 20% chance that it was due to the study drug and an 80% chance it was due to other factors?

S05: Yeah, then I think you're starting, the strength of the other drugs association is starting to drop so I would say possibly study drug and probably underlying breast cancer. [right, great]

M: And then given the choice, how would you prefer to grade causality as certain, probable, possible or unlikely or as a yes related to the study drug or no not related to the study drug.

S05: No, I think you have to kind of have a graded scale. I think yes or no becomes very hard and we're not always sure you know. And there's always that element of doubt about it. **(Lack of confidence in attributions)** But I think you have to be able to say how strong or weak your doubt is and when you have the graded scale it just gives you some flexibility to do that.

M: What would you say are some of the problems or challenges with assigning causality?

S05: Yeah, I think it's um, you know what, if you have a drug and a known mechanism of action and it's causing toxicity with those known mechanisms, that's actually fairly straightforward. So you know, you're giving the drug that has that known toxicity, the patient is taking it, the likelihood is it's the drug causing it. It's when you have, have side effects that you aren't expecting that, that may well be related to the drug just because it's being studied in a species that it 's never been studied in before and you want to be sure that you are not missing toxicities. And I think it's easy to ah, often these things only come out in the wash you know. And a good example of this is the um, the lung toxicity that we saw with the Iressa type of drugs and in fact that wasn't expected. But when you treat enough patients and if people had reported all of those as unrelated to study drug, that likely would never have come to light. **(Always need to have unexpected reactions as possibly attributable to the drug, so many unknowns)** But it was being flagged as possibly related to study medication then

when you're analyzing patients then you say, oh look 50 or more patients. So I think it is important [interruption for signature] [so you were talking about the Iressa example] yeah, so if you have kind of uncommon tox. And another one is these, funny, reversible, neurovascular events on Avastin so as we're treating more patients these events are coming up. We have to have a mechanism to make sure that if there's some question of whether there's a relationship that we, we can at some level capture that. And I think that's really the trick of making sure that we include those.

M: Can you tell me a little more about, you said, was it Avastin?

S05: Avastin it's bevacizumab it's, I can't remember the terminology, basically there's reversible vascular, it basically causes vascular [] been on the Avastin it is related to some events where you know, even if, you know the choice of it is or it isn't, if it isn't then you've kind of lost them but only in a very small way. And the other problem we have is, see, you know one of the problems with some of these studies where you, where you're looking at chemotherapy drugs combined with targeted agents that don't have, and it's really a question of, you're giving chemo drugs that we know have side effects. And then you'll see the reports come back where a patient is getting classical chemotherapy related toxicity and then they attribute this as probably related to the targeted drug that likely has no role at all to play and that's very frustrating. **(inconsistency amongst professionals is frustrating)** Because you get these reams of toxicities that we as investigators on other studies with these agents have to deal with that are just you know [... chemotherapy]. Yeah, they are really, I think in some cases we have to be, make sure that well, is there an element of doubt but clearly that's where the unlikely category comes in and these are patients who are being said, well it's probably related to their targeted agent and you know, clearly that's probably likely not the case. But what that does is it really contaminates the whole database in terms of what is the causality of these toxicities. It's a huge problem worldwide and we certainly see that when we're having to look at data from large international

studies where you have groups who probably don't have a lot of experience with either the chemo or the targeted agent. And making these attributions it really kind of make a mess of the database. **(Misattributions can have serious consequences)** [right, right]

M: So that would be one of your concerns about how clinicians are assigning causality.

S05: Yeah, we should have, I think it's important we have a standardized approach to answering causality, you know, if there was a standard algorithm you could be very famous if this works out. [well A could] Oh don't let him take all the credit. **(understands the importance of a standardized tool)**

M: Any other concerns about how clinicians assign causality?

S05: Those are kind of my major concerns, spectrum that we should have and don't do right now that I think would really be. **(Believes we should have a standardized tool)**

M: Any external influence or pressures?

S05: There's an awful lot of pressure when you're doing early phase studies with a small biotech company. They, there's a lot riding on, on, you know, there are the issues of well are you going to torpedo their only drug or just from a financial point of view, with toxicities that are going to expand the dose level. That's gets in and take longer for the study to complete, those have big financial implications. On the other hand our, our first responsibility is to the patient and if not I think making sure, a lot of pressure from the smaller companies. And I think the other pressure is just the sheer volume of the adverse events you know, here are the ones from the last couple of weeks. So it's just huge volumes and they all, and everybody wants them done within kind of 24/48 hours and it just becomes

impossible to do. **(time constraints affect confident decision making)** On some level there needs to be, and a lot of these are these ones that you know it's clearly the chemo drug and probably really isn't related to the study drug. But there's, probably half of those are those kind of things that have been generated, probably inappropriately because of the experience of the people who, it's a problem. It's a huge workload and unless we're handling them consistently I'm not sure we're going to be any further ahead. **(apprehensive about assigning causality because of the large implications a misattribution can have on a study, need consistency)**

M: The next thing I'd like to ask you is just to do a little exercise, I'm wondering if you go read over the following questions and then cross out any that you don't feel are relevant to the Phase 1 oncology trials.

S05: I think those are all relevant questions.

M: Okay, so would you be able to just rank them then in order of importance.

S05: I was afraid you were going to ask that. [I know, late in the day] And some of them are kind of going to be hard, they are all, many of them [you can use more than you know, if any are equally important then you can just] I'm just going to kind of star the most important ones. [okay] In Question 10, um, adverse event confirmed by evidence of the toxicity or what are you talking about there?

M: That's a good question. What do you interpret that as?

S05: I'd like to have it if you are saying they have hepatic toxicity and the liver function tests are going up. That's how I'm interpreting what they're meaning. [yeah] Because I would say I mean they're kind of, it's hard to kind of split them up into kind of you know, ranking them 1 to 10 but I'm just going to arbitrarily put

some numbers down, 6 & 7 they're pretty close in terms of the order you put them in. I've done this backwards, will do this. [okay, super]

M: One is least important and 10 the most important. You ranked number 7 the lowest, was the drug detected in the blood.

S05: I mean I think that of those factors, I think they were all on some level important, I just think, um, we're, we're often not clear when we're doing these studies. In humans, what are important drug levels, I mean we are often, have information on levels in, in, in animals or the, the models they've been studying but those don't necessarily correlate. So I, I put less weight on that than some of the others things. Just that we can be fooled by what we think are toxic levels are...

M: And did the reaction reappear when a placebo was given, you rated that one fairly low as well. Why is that?

S05: Again, I think in terms of the other ones, I think are stronger, is that important? Yeah, I think if it's happening when you're giving them placebo it makes it less likely it's your study drug. But I, I think all 10 of them actually are things you should use to consider, it's just a question of do I think that's as strong as if you actually give the study drug and something happens. I think that just gives me stronger evidence that's all.

M: Is there anything that, or that wasn't here that you felt should be included in this list?

S05: I guess something about the mechanism of action of the drug. There's nothing that would suggest that, that toxicity that you are seeing would be in keeping with that. [excellent, thanks]

M: And just lastly I would just like to ask you a little bit about your experience as a clinical trial researcher. [mmm hmm] So in which cancer(s) do you specialize?

S05: Gynecologic cancers.

M: You have your MD and what year did you receive your MD?

S05: 1980.

M: And what year did you receive your oncology license?

S05: 1985.

M: And have you got any other [no] anything else like that, any education to do with clinical trials?

S05: Yeah, there isn't anything no [no okay great]

M: And what year did you become involved in clinical trials as researcher?

S05: Really once, so 1986.

M: Overall, what percentage of your work time would you say is devoted to clinical trials?

S05: I would say probably about um, about a half. [50]

M: And then of that 50 percent how much of your time is devoted to clinical trials?

S05: Um, I would say $\frac{3}{4}$ of that.

M: Okay and 25% is Phase 3. [yeah] Just roughly yeah.

M: Have you ever been a local PI [mmm hmm] for a trial yeah. And can you tell me about any training you received specifically with respect to assigning causality.

S05: There hasn't been any formal training, yeah, there's hasn't been anything formal.

M: What kind of informal training have you had?

S05: We've had, certainly going to the American Society of Clinical Oncology and go to there they often have educational days where you know a lot of these issues are discussed and their, their sessions around the conduct of clinical trials. Certainly informal teaching sessions that, that I have gone to that have reviewed those aspects. ASCO is particularly the one, the other one would be the Molecular Target in Therapeutics meeting where they talk about clinical trials and they're particularly looking at is it the agents and which one of the agents is it. And so it's very complex and clearly people have given it a lot of thought.

M: What additional education about assigning causality...

S05: Well I think what would really be nice is to have, people have a standardized approach and that there are standard decision making tools that I think are accepted as you know, to make those decisions. And I think that's the problem because it's a dog's breakfast out there now.

M: We are also interviewing clinical trial nurses. Is there anyone else that you recommend I contact?

S05: Yeah, in terms of the nurses that I work with any one of the Phase I nurses A, S, M, S, H and the data manager, Y. [great, thank you]

M: That's all the questions I have. I just want to thank you for all the time you spent with me today.

S05: What's going to happen in terms of the information you're gathering. So at the end of the day what's the plan?

M: So this information, we'd like to do sort of a qualitative analysis of this data and use that to first of all inform this tool that we are developing and help us in developing that tool. And also, I mean these interviews also serve the purpose of raising awareness down the road. So what we're going to do is we'll definitely give you an executive summary once we've got things summarized.

S05: Is the plan ultimately to develop a tool for this [yes] or to use a tool that's already existing.

M: Well you know, yeah, that's sort of what we're looking at now, the Naranjo tool is just one that's out there and A felt that it needs to be modified so we might just modify the Naranjo tool. Okay.

S05: Good, excellent.

Subject 06

M: Alright, so even the most experienced clinicians find assigning causality to adverse events challenging and many groups, such as industry sponsors, clinical trial cooperative groups, research ethics boards, they all expect prompt and sensible causality assessments. But as you know, assigning causality isn't that straightforward, and if its done poorly it can have large implications both for patient safety or drug development. So we're interested in developing a tool to help clinicians efficiently and reliably assign causality specifically during Phase 1

oncology clinical trials. And we feel that by better understanding your needs as a clinician we can make our tool more relevant to you. Do you have any questions. [no] No alright. So let's just say one of your Phase 1 clinical trial patient experiences an adverse event. Can you please walk me through how the situation is handled?

S06: So in the Phase 1 setting our priority is to document toxicities and so I'll have an emphasis on assessing patients on a fairly frequent basis for a variety of toxicities through using. And so any, obviously any grade 3 or 4 toxicities are picked up so the trial needs to be set up in such a way that you're carefully, frequently assessing people so that you can document any 3 or 4 grades of toxicity and then make a determination. We will tend to document and report most of them, basically even if most of them are unrelated. **(not all Aes are documented)** That's, we're kind of in a spirit of or an atmosphere of well the majority are unrelated. **(mindset that AEs are not related)**

M: And so how do [so we err on the side of caution] yeah. How do you actually determine causality when you're thinking about those adverse drug events? What sort of thinking do you use?

S06: That is a challenge in that typically when patients go in to clinical Phase 1 trials they have advanced, often refractory cancers and ah, needless to say, significant ah, medical problems at the beginning and throughout the clinical trial. **(assigning causality is difficult)** So, so definitely is a challenge, um, often times patient's cancers are progressing resulting in symptoms, problems that if you send somebody out um and they have grade 3 or 4 toxicities because of progressive cancer or because, basically all one can really do is, based on experience of managing these people sort of know what to expect as their cancers progress and as their regional stages of life, as in previous experience in managing. And then if a new toxicity comes up that one hasn't seen before you would tend to look at the intervention. It's really based on experience at this, at

this stage. So really it would depend on a, an experienced investigator who has managed a lot of the specific patient population to in my opinion, accurately determine if this is something that's related. **(Feels experience plays a crucial role)**

M: Do you look at what is ...

S06: So, sorry, the mechanisms I'll look at is the timing of the event. The relationship to the administration of the drug, whether it's, whether the toxicity has been previously, seen at previous cycles of the drug but in a milder form. And also in my mind I assess whether the event seen is related to a short-term effect of the drug or potential long-term effect of the drug. Short-term effects tend to be easier because there is that temporal relationship. The longer term effects of the drug, aren't you know the first weeks I think are more challenging. **(places strong emphasis on temporal relations)**

M: Can you give me an example of a longer term?

S06: Um, I mean an example would be of um, Adriamycin, a chemotherapy drug resulting in heart failure from toxicity. But you know, if you were investigating you probably wouldn't be seeing it on each cycle, it would only be after the fact. But I think one, one breaks it down into short-term and long-term effects that need to be documented and. And I think trials are often set up more for short-term.

M: What are the resources you refer to when assigning causality? I guess knowledge of working with that patient population, any other resources?

S06: Well, I mean if, to investigate the adverse event, I mean as a clinician I have to treat the adverse event because I'm responsible for managing the patient so I would use the lab, the um, um, any you know pre-clinicalPubmed to determine if it's related. **(assumes responsibility for patient)** Sometimes I'll go

to other investigators on the trial to see if they've seen if they've seen similar events. [your local investigators here or at other sites?] well it depends, yeah at other sites. Yeah, just send out a broad email to [with email yeah] Yeah. [do you find they're generally pretty helpful] Yeah, I think, I think in a clinical situation if you, if you, you know, I have a patient whose developed a certain problem, has anyone seen this?, people are often very willing to give their opinions. And often times someone will say yeah, that's funny we've seen that as well. **(seeks support/confirmation from others)** I think also if one's running a trial, sort of frequent investigator conference calls just to hear those types of words are, is very helpful. If someone has a sense about something you can kind of discuss it that way. So I very much think working as an investigator, working in isolation. **(feels isolated, seeks support)**

M: Do you use any tools, or what sort of tools do you use to help you assign causality, do you use a formal algorithm?

S06: ... or list, no I'm not aware of any.

M: What sort of general ...

S06: Sorry, to back up on that one I do, we do sort of adhere to a dose finding study process in that if somebody develops grade 3 or 4 toxicity we will either treat at that dose for another group of patients or reduce the dose. I mean one follows the protocol for dose limiting toxicity. So one does work within those.

M: What general guidelines do you follow when assigning causality, are there any rules of thumb that you tend to use?

S06: Well I, I follow, as dictated in the protocol I follow the you know, the notification and the definitions in the protocol for ah, so it will be, will be, that

information will be present in, in definitions in the protocol. So I will go back to the protocol and read.

M: Does the protocol sort of give you guidelines on how to assign causality?

S06: No, no, well it just gives definitions, so um, [what's an SAE, what's an AE, when to report, what the timelines are] the timing and who, specifically who needs to be called. So that the um, um, [flipping paper] there must be one here, you know um, again the definitions for adverse reaction to therapy, unexpected adverse reaction to therapy, expected adverse reaction to therapy, what is an SAE, results in death, is life threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant. So I, I do tend to go to the protocol and, and determine the clinical situation and how it fits into those definitions. That's about all I'll do though, I don't have any other.
(considers process of attributing causality to be minimal)

M: No real guidance on assigning causality, that's sort of left up to you.

S06: That's a clinical judgment based on what's happened to the patient.

M: You said that you know, you tend to err on the side of caution.

S06: I think whenever, whenever a grade 3 or 4 toxicity is documented this one little, I'll, I'll try it, especially in Phase 1, you know, onset date, resolution date, I'll try to document all those things. Often it's not just the one case but a series of cases over time and when there's a review by the protocol safety committee if there's something going on it gets picked up. I don't have anything at the bedside where I can, a tool that I can look at and sort of help me determine **(no tool, but it would be helpful)**

M: Do you think that would be helpful?

S06: Mmm hmm.

M: Yeah? [yeah] What do you consider to be the most important factor when you're assigning causality?

S06: Timing. **(again strong emphasis on timing on an event)**

M: Could you sort of expand on that, can you give me an example of when the timing would...

S06: Well it depends on the nature, the nature of the drug and mechanism of how it works but, but I mean certainly if the drug is given and in 8 hours something occurs I would want to tend to think it's the drug. Somehow it's had a role in what's going on, I think that's the most important. Second would be, you know, what is the mechanism of action of the drug? So if a drug is an angio, angiogenic drug and all of a sudden I'm seeing bad neuropathies then I know in my mind that the two are related based on the mechanism of action of that drug.

M: Now I would just like to ask you to consider the following scenario. [okay] Let's say you're treating a 65-year-old female patient with a confirmed diagnosis of metastatic breast cancer. And she's on a Phase 1 trial with a new investigational drug and that's all you know but she experiences a pulmonary embolism. How would you assign causality to the study drug if you knew that there was a 75% chance that it was due to the study drug and a 25% chance that it was due to other factors, concomitant [10:12 not sure if finished]. [um] Sorry and given, I'm sorry I didn't give you the grading scale, but let's say the scale is certain, probable, possible or unlikely.

S06: I mean it's, obviously that's a tough question because metastatic cancer patients are at risk of PE, so in itself then I think that has to be documented as an

SAE. In terms of defining causality you have to have the patient's history, the various risk factors beyond their cancer for pulmonary embolism, risk of pulmonary embolism based on other medical history. To me that, that, this [?] something the patient was ultimately at risk for having a PE [11:00] [So probable]

M: Let's say there was a 50% chance that the adverse event was due to the study drug and 50% chance it was due to other factors? And given the same scale, certain, probable, possible or unlikely.

S06: It would still be probable [11:14]

M: That's actually my next question, let's say there was a 20% chance it was due to the study drug and an 80% chance it was due to other factors? Possible?

S06: Possible.

M: What, what would it take then for you to say that it was unlikely? What would be your percentage?

S06: Oh, I mean in the cancer setting it would be clearly due to progression, something that clearly in my mind is related to the existing cancer then I would call it unlikely, everything else would be called possible or probable. It's just that the Phase 1 mentality is pretty much to overcall everything and then review that data. **(mindset to err on the side of caution and attribute AEs to the drug)** You know, if you're not calling it possible then you're not going to see it and one of the side effects of the drug called Thalidomide we use for multiple myeloma is PE, and that really wasn't recognized until the drug was well into use. And I think your example is a good one I think people could easily brush it off and if a bunch of people do that, you never realize that actually 20% of the people on Thalidomide get it and that's why you get overcalling.

M: In the case of Thalidomide it didn't get discovered until much later?

S06: Yeah, it was kind of discovered through you know trials being completed and then people looking saying, boy that's a lot of clots and then the drug is being used now for a decade and it's really only in the last two years people have been taking steps and it's because, PE is a good example, it's something that happens in the cancer setting and clearly it's an example where if one had called it SAEs and all the people participating in the Phase 1 studies had called it an SAE possibly related then it would have been picked up much earlier. **(reporting improves patient safety)**

M: And they're using thalidomide to treat which type of cancer?

S06: Multiple myeloma, among others, the primary one for us is multiple myeloma [when did they start using that again?] 13:12

M: Given the choice, would you prefer to grade causality as certain, probable, possible and unlikely or as yes related to the study drug and no not related to the study drug.

S06: Um, I'm comfortable with the previous one, the first one [the scale] yeah, um, it provides a bit more information. But at the same time you're right, is it or isn't it? I think it's better to maintain a sort of a graded scale because I don't think one can be that definitive. With the number of resources you have, it's only a matter of being able to document and have there as a possibility. **(never really a concrete answer)**

M: What would you say are some of the problems or challenges with assigning causality?

S06: Um, I would say that more resources would be good for investigators, more resources at their disposal. [what sort of resources] **(not enough resources available)** Well, resources through the sponsor [for what] for information [oh okay] more information as to whether, you know, if you have questions about a certain event. And for example you wanted to understand the drug's pharmacology better and try and determine you know, in some way could there be access to that information beyond the IB. The opportunity to discuss on a regular basis with other investigators, how the trial is going, um, through conference calls is a good idea. **(need for an open forum between investigators)** And you know, I don't know how a tool is, is formulated, there's nothing to my knowledge to say a meta, you know a 65 year old metastatic breast cancer patient, what is her risk of a pulmonary embolism by any drug? [yeah] But you know, that, that would be my, in determining causality, that would be my first step. And so if the chance of her having a PE was 2% then I would lean towards giving the drug more. If the chance of that was 80% as you had said, but getting that information available to you is [basic baseline risks and] . Yeah, for, for various SAEs, what is the risk of ah, ah, how often do metastatic cancer patients get severe headache, how often do they get um, the other SAEs that are involved.

M: Any other problems or challenges that you've encountered when you are trying to assign causality?

S06: Um, well there, you know, there, I think one has to fight, now this is a more of a perception, I don't have any examples. But there's a risk that the sponsor may want, may prefer you to go to an unlikely conclusion. That I disagree with. **(feels pressured by sponsors)**

M: Have you ever personally felt that?

S06: No I haven't because I've stubbornly just said well that's my final answer, so I've never felt any, any sense of coercion. Obviously, you know, inherently results in more work for somebody but ah, in the Phase 1 setting I, I, I think ultimately it's the sponsor's in their best interest to fully understand what their drug is doing and what it's potential effects are. But one does have to be fairly stubborn in that regard. [interruption, taking a quick call] **(Feels they need to defend their decisions)**

M: So what are some of your concerns about how clinicians currently assign causality?

S06: Lack of appropriate information. **(not enough resources)**

M: What kind of appropriate information?

S06: Well information about the patient.

M: They just might not have enough details about the patient why is that?

S06: Well I think if there's a, I think there is a certain distance often between the clinical trials nurse and the physician. Clinical trials nurses at least locally do a fantastic job of being very involved in the patients. I think there's a risk of um, them not seeing the big picture on certain issues or missing. So information is important about the patient about the drug about the situation. **(need a holistic perspective on the trial)**

M: Is that just because the clinical trials nurse hasn't collected it or it's just not available or?

S06: Well they pretty much have to collect it if they're using the Common Toxicity Criteria tool, they have to document ah, certain things, not all of them. I'm not

always sure if the PI of a trial is available to get that information always in a timely way. And when it's an obvious adverse event then yes, but it's the smaller ones that I'm not sure are always being, I'd say the first thing is information, patient information, information about the event. All the literature that goes around the risks of that patient having that event on their own and then all the information about the drug, the pre-clinical, investigator drug brochure and communication with other investigators and company. [yeah, a lot of things go into it] So all of those things need to happen and all of them sort of intrinsically have their own, not show stopping, but little obstacles that don't prevent it so. Okay, well tell me about the drug, okay, where's the IDB, why isn't it in my office. I want to talk to the sponsor about the drug, oh they're on holidays, they'll be back in two weeks, okay, well who's covering them. **(run into obstacles, slows down causality assessment)** You know, then we have a conference call about the study with all the investigators from other sites [right] and if they were happening frequently then there would be you know, a venue to be able to discuss these things. [right] **(lack of communication)**

M: From your perspective then what would make assigning causality easier than regular conference calls.

S06: Access to information, I mean I think a tool would make it easier, I'm just, at this stage don't have a vision of what, a, a, phenotype of that tool, how it would be. Would it be a, purely information based, the patient has toxicity A in the setting of disease B, plug into a formula, what is the risk of this happening. If it's greater than 10% it's probably the disease if it's less than 10% it could be the drug. [right] I, I suppose, although I can't sort of envision how, that would be a huge database to capture all the potential toxicities or adverse events in a setting of a specific cancer type, maybe, I don't know. But that would be helpful yes.

M: What I'd like you to do now is a little exercise for me. I'd like you to read the following questions and then just cross out any that you feel are not relevant to

the Phase 1 oncology clinical trial setting. [and put a number] Well after that I'm going to ask you to rank them in order of importance, so 1 would be least important [so cross out the ones that aren't important] yeah. So first just cross out whatever ones you think aren't important. [okay] And then if you could just rank the remaining questions in order of importance, so 10 would be most important and 1 would be least important. [right, I don't know what 10 means] Just that that's most important to you as a, as a consideration when you're assigning causality. [okay] Okay, great, thank you. Okay, so I see that you crossed out number 6, did the reaction reappear when a placebo was given, why did you cross that one out.

S06: I don't think I'd, that would be done [no] that doesn't make sense to me. You wouldn't have a drug, a patient on a study drug, they have a reaction and then give them a sugar pill to see if they have the reaction.

M: What about number 8, was the reaction more severe when the dose was increased, or less severe when the dose was decreased, I mean.

S06: So if a person had a reaction to a certain drug, you wouldn't go back and give them a higher dose of the drug.

M: Would you decrease the dose and see if?

S06: If, sometimes the protocol would specify if there was concern to give half the dose, um, but that implies that their reactions were completely dose related and often times reactions aren't dose related. It's not always a dose phenomenon so I don't see that as relevant.

M: Alright, and the one that you ranked the highest was number 8, was the drug detected in the blood? [oh I'm sorry I did it backwards] oh you did it backwards.

S06: Well I saw the scale and you said rank and I thought, I thought the scale was going to happen later. So you've got to do them all backwards now.

M: Okay, I won't make you do it again. So in your mind then number 2 is the most important did the adverse even appear after the suspected drug was administered? [yeah] Okay, alright, great. And was there anything on this scale, any questions here, or anything that you thought that was sort of missing that maybe should have been included that wasn't there?

S06: I thought that was pretty comprehensive, those seemed to be the right questions, except for 6 and 8.

M: So lastly then I would just like to ask you a little bit about your experience as a clinical trial researcher. [mmm hmm] So you're a hematologist and what cancers do you specialize in?

S06: Multiple melanoma, Non-Hodgkin's lymphoma.

M: And what year did you receive your MD?

S06: 1988

M: And what year did you receive your hematology license?

S06: 1991

M: And have you ever taken a Masters in Clin Epi?

S06: No

M: Is there any other research related education that you've had?

S06: A three-year fellowship.

M: And when did you complete that?

S06: That was 96.

M: Where did you do that, was that NCIC?

S06: It was an NCIC fellowship.

M: And what year did you become involved in clinical trials as researcher?

S06: 98.

M: Overall, what percentage of your work time would you say is devoted to clinical trials?

S06: 20%.

M: And of that what percent of that is devoted to working on Phase 1 or 2 trials?

S06: 80%

M: And then the other 20% would be Phase 3?

S06: Ah, Phase 2 or 3.

M: Okay, so 80% is strictly Phase 1.[Yeah]

M: And have you every been a local PI? [yeah]

M: So now I'd like to ask you a little bit about the education that you've have received specifically around assigning causality to adverse events. So can you tell me about any training that you've have received specifically with respect to assigning causality [none] to adverse events? Anything informal?

S06: Oh, through the clinical trials methodology group, I've had interactions in working with them [the group here] yeah, through M L. When I write protocols, I see more of a science, scientist phenotype and as a translational researcher and writing and designing protocols that first hand experience is valuable in the processes. [so that group has really helped you out] yeah [in doing that] yeah.

M: Any additional education about assigning causality that you feel needs to be made available to clinicians?

S06: Well I think, you know it's, I think, I think the process of understanding the Phase 1 study and toxicities and documentation and reporting SAEs probably would lend itself to some form of workshop or short course so that people do understand the general principals and how things need to be done. Um, in terms of actually running the trial you know the devil is in the details you would have to have it all set up appropriately so that basically everything runs on auto pilot once you have a protocol there. And not sure if one is you know, doing a Masters in Epi, I'm not sure you learn those specific details of, you know, you know, that's the realities and those are the details you need to focus on. So it is experience. And I think you know, REB boards need you know, have to be the guardians of protocols that you know, there is some recognizing that this trial, especially if it's a local investigator trial has the necessary infrastructure in place to be able to document and capture all the information. I think, you know, I think the academic institution at the same time should be able to provide that infrastructure at least in support, if not through collaboration with the groups. The challenge is that the good Epi group who can run trials in an academic setting are going to be

approached by drug companies. And you need a lot of money, those staff have to be paid and there are costs to the clin epi group and that's a lot better than a local academic investigator say getting a grant for 100,000 bucks and he can give you a \$1000 bucks. I think they're, they're, the risk I think comes in the academic setting when the institute needs to kind of step up I mean today that's being done, certainly here's its done so it's, but I don't know about other centres across the country. **(funding plays a major role)**

M: So we're also interested in interviewing clinical trial nurses [mmm hmm] is there anyone you could recommend I speak with.

S06: The two I work with are KH and TH.

M: I think that's all the questions I have so thank you very much.

Subject 07

M: Alright, so even the most experienced clinicians find assigning causality to adverse events challenging and many groups, such as industry sponsors, clinical trial cooperative groups, research ethics boards, they all expect prompt and sensible causality assessments. [mmm hmm] But as you know, causality, assigning causality isn't that straightforward, and if done poorly it can have large implications both for patient safety and also new drug development. [mmm hmm] So we're interested in developing a tool to help clinicians efficiently and reliably assign causality to adverse events that occur during Phase 1 oncology clinical trials. And we feel that by better understanding your needs as a clinician we can make this tool more relevant to you. [okay] Do you have any questions then before we start? [no] No okay. So let's just say one of your Phase 1 clinical trial patient has just reported experiencing an adverse event. [mmm hmm] Can you please walk me through how the situation is handled?

S07: So you interview them, you ask them what the side effect was you would immediately grade it, 1, 2, 3, 4. Um, then depending on the severity you treat it,

usually 1, 2 you don't, it all depends what it is right. But the higher, the higher the causality probably the more attention you pay to that particular adverse event. [the greater the severity] The greater the severity. **(more attention paid to severe AEs)** So you make sure the person is safe and that um, you treat that. Now do you want to get into notifying the sponsors and things like that. [right] So what you would do [if it was a serious adverse event] yes, serious adverse event, obviously you would look to the protocol as to how you're going to report it right. Some grade 3, 4 toxicities if they're unrelated, um, they don't want to know about it but usually in Phase 1 they want every single detail. So if it's a serious adverse event obviously you follow protocol and notify the company within the 24-hour time required. If, you know, if it's a non-serious but you know, whatever, if it's a non-serious event you look to the protocol to see whether you're supposed to stop the drug, if you're supposed to reduce the drug and sometimes they give guidelines so you have to look to the protocol to see.

M: What about in terms of assigning causality?

S07: Assigning causality is some, I would say a combined event between the investigator and the study nurse. **(assigning causality is a team effort)** I think both parties can, give valuable information as to their insights into the, into the whole situation. Obviously the principal investigator has sort of ultimately authority as to how he or she wants to assign, assign that causality. However, I really feel that, like we kind of work together to assign that particular causality. If the patients comes with grade 2 shortness of breath or something like that well why are they having the shortness of breath. [right] And is it just because it's pre-existing or is it because of what we're doing to them and we'll have a discussion about that. [so it's a joint effort] Yeah, I would say so.

M: What are the resources you refer to when assigning causality?

S07: The ah, book [oh, when you're grading you mean?] yes [okay, so that's for grading the adverse event] grading the adverse event. And you said resources to assign causality?

M: Yeah, when you're actually thinking about whether the drug is related to that adverse, whether that adverse event is actually related.

S07: If it was actually related to it or not? You would look at the protocol and look at the research that has been done on the drug to see if this is something that has been reported before. And if it, that, that would be the major resource. [and most of that's in the protocol?] Yeah, usually in the protocol, or usually the PI has articles that they have. And also, the resources being past experience as well in this particular drug which was kind of similar to this one.

M: Now in terms of, you mentioned the common toxicity criteria which is sort of a tool that you use to grade [mmm hmm] the adverse event. What tools do you use to help you assign causality?

S07: Assign causality, didn't we just sort of answer that? [yeah, yeah] Using the protocol, using the research.

M: Those are the resources that you go to, that you refer to.

S:07 How do you come about to assign causality?

M: Yeah, do you use any sort of flow sheets or decision trees?

S07: No we just kind of go is it related, is it not related, is it somewhere halfway in-between and sometimes it's, it's obvious. You know, the person had a pre-existing asthma or something like that. And usually you take a base, the way we usually do it is we take what they were at baseline and if we've made them worse

we have to then decide, okay, is that because of the drug, the disease or just them right? But as for decision trees and things like that no.

M: And then are there any sort of general guidelines that you follow when you assign causality, any rules of thumb that you use? [laughter]

S07: No not really, using just yeah, anything.

M: Let's say for example it's, let's say it's an adverse event that has occurred with a patient with a headache say [mmm hmm] and they reported that they had the occasional headache at baseline [mmm hmm] and these seem to be maybe more frequent how would you sort of [how would you assign causality to that?]. Yeah, like is there [so you] any sort of general rules that you might use?

S07: Well, has it happened before [right] if it's happened before and you've kind of got these cluster headaches and if it is definitely increasing intensity, the adverse event is increasing we would, that kind of raises the red flag that it could probably either be possibly or, or probably related to the particular study medication. We're always concerned when anything increases, is it because of the study drug or not? Or is it just because of the nature of their disease? If you have brain mets and their disease is increasing you're going to have more headaches. So you kind of have to take the whole picture of what's happening with the patient and their disease as well as their response to the medication as well as their pre-existing whole picture [right] when assigning causality. **(need holistic perspective)**

M: Of those factors, what do you feel is the most important factor when assigning causality?

S07: Um, [or is it hard to say] I think you have to take the whole picture, I think you have to take the person and their pre-existing disease and the study medication.

M: When you say study medication, what is it about the study medication that you're...

S07: Any kind of side effects [that is known about it] that is known about it yeah.

M: Now I would just like to ask you to consider a scenario for me. [okay] Let's say you're treating a 65-year-old female patient [mmm hmm] and she's got a confirmed diagnosis of metastatic breast cancer. [mmm hmm] And she's in a Phase 1 clinical trial with a new investigational drug and she experiences a pulmonary embolism. [mmm hmm] Now how would you assign causality to the study drug if there was a 75% chance that the adverse event, the pulmonary embolism was due to the study medication and a 25% chance that it was due to other factors say [have cancer or whatever] yeah, disease progression, concomitant meds, concomitant illness. [mmm hmm] And the grade was, the scale is certain, probable, possible or unlikely.

S07: I would probably say probable, just because you can't be certain because you have the 75 versus the 25 and the 3 to 1 sort of thing. And because it's 3 to 1 it's more probable that it's the study medication itself.

M: Now what if there was a 50% chance that the adverse event was due to the study medication and 50% chance it was due to other factors? Then using that same scale how would you...

S07: Then you would go somewhere in the middle there, possible [one down from probable] one down from probable.

M: And then let's say there was a 20% chance that the adverse event was due to the study medication and an 80% chance it was due to other factors?

S07: Third one right because you don't want to, and that's, I would probably go unlikely/possible. It's an 80/20 but you always want to be on the cautious side, well maybe, you have to look at other patients as well, how many of those are getting blood clots as well. So when assigning causality it's kind of hard because you don't know what's happening with the other patients as well. So anyway, we'll go unlikely.

M: What would you say then is your threshold for you know going somewhere in-between possible and unlikely. What is the percentage chance for unlikely?

S07: To assign it to unlikely, yeah, probably about 20% and lower yeah, probably yeah. Like, hindsight is always 20/20 right. You can assign causality but you know if every single person on the study is getting a blood clot then obviously then you would, you would relook at your causality as well. It's really hard at the time to go definitely for sure this is unlikely related. [yeah] But anyway.

M: You said it's important to know what's going on with the other patients [mmm hmm] in the trial, how do you keep abreast of that?

S07: Well usually there's teleconferences and other meetings to discuss what's happening with other patients. But a lot of times communication isn't as good as it could be. **(lack of communication)**

M: Who are those teleconferences with?

S07: The principal investigators usually. The PMH consortium is quite good with their teleconferences. NCIC as well is that, study nurses are usually not as involved with the NCI.

M: But you get to sit in on the ones in the PMH?

S07: Yeah we actually get to um, yeah so I think that's kind of insightful. We should be involved in as much of those discussions just so everybody is informed. I haven't done a lot of, so I don't know what they do to keep it up but sometimes you do feel a little bit, you have no idea what the other people are doing. And it would be a little insightful as to how they're doing it, yeah. **(feels uninvolved in certain aspects of the trial, secluded)**

M: And given the choice, would you prefer to grade causality as certain, probable, possible and unlikely or as a yes related to the study drug or no not related to the study drug.

S07: Oh I love grey areas so the first one. The other one seems too definite [yeah] it's really hard to say yes or no because you don't really know, it's just one of those could be couldn't be, yeah.

M: What would you say are some of the problems or challenges associated with assigning causality?

S07: Problems, first of all you're never definite, definite, hindsight's always 20/20, so looking back a few months later you can sometimes get a more clearer picture of what, like analyze the situation a little bit more. Sometimes when you're right in the situation and you have to, you have that responsibility of assigning it right then and there, you don't have all the information right? You don't know how it's going to end, you don't know, um, if, if, why it happened or anything. You can analyze the situation after it occurred and everything has evolved then it's sometimes easier to go back and go well this and this happened we can do that. So assigning causality sometimes at the time is sometimes clear cut and sometimes very difficult. **(easier to assess over time)**

M: Do you ever have to go back and change your?

S07: Oh absolutely, where we, something may have been unlikely or and then we decide later on that no it's probably related to the study drug.

M: And what are some of your concerns about how clinicians currently assign causality.

S07: I don't think we pay a lot of, as much attention to the importance of it as we should. I think a lot of times, causality is, is the minor things, the minor things that nobody kind of pays attention. Major things are usually, if it's an SAE you can pay a lot of attention to is it related, is it not, but the grade 2 things sometimes the nurse just kind of assigns causality and the physician will look at it and may change something. But as study nurses we try the best we can to assign causality, um, with the physicians, like obviously we're going to ask for the guidance but for the minor things we don't. **(feels not enough attention is given to minor reactions)**

M: So in your experience then do you tend to only go to the physician when it's a serious adverse event or do you discuss causality with the investigator for all of the adverse events?

S07: For all the adverse events no. [just adverse events] Just adverse events, anything grade 3ish, we definitely, ah, 3 or above, definitely I would consult the physician. It's those grade 1, 2's that I usually assign causality based on the information available on that particular agent. **(feels they need to seek consultation for more serious AEs, minor AEs are not an issue)**

M: What do you think the implications are of that, like why are you [hopefully we are right] yeah, but why are you concerned about that?

S07: Why, because you know what, um, it's those minor things that can cause good quality of life issues in patients. And if somebody has bone pain because of a particular medication, one bone pain is, two bone pain, that's starting to implicate on quality of life issues. And if we're kind of assigning bone pain, you know that could have issues and we may not like notice the issue until later on in the development of the drug. So I think it is important to have a good idea if a drug causes a certain side effect or not, no matter if it's mild or severe. We're always concerned about the moderate to severe but we're not..

M: Have you ever, or what external influences or pressures from third parties have you felt when assigning causality?

S07: Not too much, but then again I'm not the one that the sponsors contacting when they call you and go are you sure that this is what you think it is? and stuff like that. I've had one of those calls where they'll call back and they'll say is this the way you want it? And you just go back to the physician and tell them they want to reconsider. And sometimes the physician is, will stick to their guns and sometimes they will re-think it or whatever [Do you find that seems to differ depending on the PI?] totally [does it?] I think so, some principal investigators are um, much more involved in assigning and how ? they are about the particular agent or their prior experience and back down, or if they'll stick to the way they originally assigned the causality. **(individual variation when dealing with sponsors)**

M: Any other influences or pressures that you [no] when assigning causality. [no] And from your perspective, what would make assigning causality easier?

S07: You know, actually, the way, when you said like a, having a tool, like a flowsheet sometimes to kind of guide you through causality. Everybody has their own kind of mental picture of when they're going through causality. But

sometimes something solid on paper, but given that though, sometimes there are always exceptional cases where you kind of have to think outside the algorithm [right] or things like that. So you always, like even you may have an algorithm for a particular situation as well, so it would be helpful, but it shouldn't kind of stifle, it shouldn't stifle the way you assign causality. **(tool won't always apply- exceptional situations)**

M: What would sort of stifle it?

S07: Oh, who knows, whenever you get an algorithm it's always like the yes/no's sorts of things and sometimes there's a grey in-between. So sometimes you have to kind of think differently. **(need to change mind frame when assigning causality)**

M: Okay, what I'd like to ask you now is if you wouldn't mind taking a read, reading over these questions and then crossing out any that you feel are not relevant to the Phase 1 oncology clinical trial setting. That's great [okay] yeah, so these questions are to be used sort of when you are assessing causality in a Phase 1 oncology clinical trial setting.

And now if you could just rank them from sort of least important to most important if you don't mind, so 1 is least important, 10 is most important.

S07: And you can assign them, it doesn't have to be 10, 9, 8 [no they don't have to be] okay that's fine. I think they're all 10, I have to think about it, okay.

M: That's good, okay, great.

S07: Yeah sure, instead of just making them all 10's.

M: So you think they're all pretty important.

S07: Yeah, I think they're all very important.

M: And then the one that you ranked the lowest was did the reaction reappear when a placebo was given? And why, why did you rank that one lower?

S07: Why did I, because something had to be lower. You know, it's still important to know, like I didn't actually rate this, like power of the mind is huge right, so you tell somebody they're going to get a skin rash and you give them a placebo and they get a skin rash right. You know, it's the power of the mind so it's, I think it's, yeah, that would be important but usually, sometimes in Phase 1 trials you don't have the placebo right, so you don't know. [right]

M: Now, what additional questions do you feel should be added here?

S07: Does the patient feel, how does the patient feel and their side effects. Does the patient feel that this happened before or is this something, a totally new experience for them? And now granted, the power of the mind is, is, is there and that if you give them a consent form and tell them they're going to get all these side effects they're going to be worried about that. But it's also insightful to know how the patient feels and how their quality of life is, is affected as well.

M: Great, that was actually a tool that was developed by a researcher named Naranjo [mmm hmm] and we're considering potentially using something like this and maybe modifying it a bit so that it's applicable to the Phase 1 oncology [oh very good] setting.

M: So then lastly I would just like to ask you a few questions about your experience as a clinical trials researcher. [sure] So in which cancer(s) do you specialize?

S07: Hematology, lung, those are the major ones right now.

M: You have a Bachelors in Nursing?

S07: Yes.

M: And when did you get that one, what year?

S07: 95 [95]

M: And when did you get your license, your RN license?

S07: 95.

M: And you're working on your nurse practitioners?

S07: Acute care nurse practitioners, my Masters.

M: And so when do you hope to have that one finished.

S07: Next year [2007] yeah.

M: And is there anything, any other sort of certifications or fellowships, anything that you've done related to clinical trials?

S07: I have the oncology nursing certificate.

M: When did you get that?

S07: The CONC, that was 99.

M: So what year did you become involved in clinical trials as researcher?

S07: 99 [99]

M: Overall, what percentage of your work time would you say is devoted to clinical trials?

S07: 100% [100%] yeah.

M: And then what percent of that is devoted to work on Phase 1 or 2 trials?

S07: Right now about 25, 25 to 50, it varies.

M: Okay and the other 75 would be on Phase 3.

S07: Let's just see what I have right now, ah, right now 50% I would say, I would say 50% right at the moment.

M: And then lastly I would just like to ask a little bit about the education you have received specifically around assigning causality. [mmm hmm] So can you tell me about any training you have received with respect to assigning causality to adverse events specifically?

S07: Nothing formal. Sometimes in start up meetings or something like that they'll, they'll say a little blurb about assigning causality but they won't really give like formal education as to what, we should use this tool or anything like that. It's mostly a set reaction sort of.

M: Anything, any other sort of informal education you can think of?

S07: You know, sometimes NCIC meetings or something like that, um, I can't say I've ever been to one.

M: So what sort of additional education about assigning causality do you feel needs to be made available to clinicians?

S07: Just the importance of it. Um, I think a lot of times we give them the case report forms and they just sign it. There's a few physicians that will check the causality that has been reported, they're kind of few and far between. I think for the majority of physicians they just sign the piece of paper. **(feel physicians do not put in enough effort)**

M: What about for people such as yourself, clinicians such as yourself?

S07: Um, be more aware of the drug side effects. Usually through start up meetings or whatever like that, we as nurses, we have to be aware of the side effects, how to manage them and what is expected and not expected. And having a more formal decision meeting with them or something like that in which we can be in the process as well.

M: We're interviewing both clinical trial nurses and medical oncologists and hematologists. I think we've probably interviewed or approached most of the people at JCC [mmm hmm], is there anyone that you can recommend that I speak to in addition to Dr. W and Dr. .L [hmm you have them] too busy.

S07: Dr. W she does some clinical studies and in the Hamilton area or are you just

M: Well we're also going to go to some other sites but for now we have ethics approval here, in Kingston and BC, [oh, that's awesome] yeah I just need to get them all lined up in the same week which is difficult. [yeah, that's all I can think of]

Subject 08

M: So I'll just explain to you what it is we are doing. We are looking at the way investigators assign causality to adverse events that occur in specifically Phase 1 oncology clinical trials. And as you know, even the most experienced clinicians find assigning causality challenging and, but many groups, such as industry sponsors, clinical trial cooperative groups, research ethics boards, they all expect prompt and sensible causality assessments. But assigning causality is not always straightforward, and if done poorly it can have large implications for patient safety and/or new drug development. So we're interested in developing a tool that will help clinicians efficiently and reliably assign causality during Phase 1 oncology clinical trials. And so we feel that by better understanding your needs as a clinician we can use that information to make our tool more relevant to you. Do you have any questions before we start? [no] No? okay. So first I would just like to better understand the clinical reasoning that you use when assigning causality. So let's say one of your Phase 1 clinical trial patients experiences an adverse event. Can you just walk me through [yeah] how the situation is handled?

S08: Um, you mean how do I think about the issue of causality? I mean the first thing really is, is there a temporal relationship, so I mean, does the side effect appear at a time that is reasonably related to the administration of the drug. I mean the second thing is does it fit in um, because often I mean if we're talking about Phase 1, it may be a Phase 1 trial just with a new agent on it's own, or it maybe a Phase 1 of a new agent in combination with existing agents. So is this an expected side effect from the existing agent. [okay] You know, is this something that's already been observed, so is it expected from the, the experimental agent. Is this something that you might expect to happen as a result of the disease, so you know, is it more a disease related symptom rather than an adverse event from the, from the drug. But the, the bottom, the difficulty is that often, you know, particularly the Phase 1 trials that I've been involved with have often looked at combining a new agent with chemotherapy. And so you have overlapping toxicities and you're left with ultimately a situation where if a patient experiences an adverse event and if you're not sure, sometimes you think, well

okay, this is, these are side effects we see with treatment and so you think well it is possibly related or probably related. But then there are things that happen that aren't necessarily related to the disease, um, aren't necessarily known side effects. And you sort of think or left thinking well maybe they are totally unrelated but you end of saying it's possibly related because you can't rule out the possibility. So sometimes it comes down to you really don't know and you know, my approach is if I really don't know and there's not a clear cut explanation then I have to say that it's possibly related. **(Errs on the side of caution and attributes to the drug when unsure)** And the difficulty is that sometimes some Phase 1 trials give you the option of saying you know, unlikely, possibly, probably, definitely you know, or unrelated. And then others it's just a simple yes/no[right] and the yes/no's are hard because you know, unless you can say it's definitely unrelated then it's yes and you know, that doesn't give you the gradation.

M: Yeah, so you definitely prefer the scale then? [hmm mmm]

S08: Um, and then there are some things that add strength to the sort of associations and so if you treat somebody, you know, particularly if somebody is getting sort of cyclic treatment instead of continuous treatment and they get the same things happen with each cycle of therapy then it's much easier, you know, to say there's an association with the treatment you're giving. So I guess re-treatment or re-challenge is clearly a fact that helps in determining causality but it doesn't necessarily help the first time it happens.

M: What sort of resources do you refer to when you're assigning causality? I know you said you think about whether it's expected

S08: Well I think it's based on what's been listed in the protocol and possibly the investigator brochure. But really do you have time to look at an investigator brochure every time? no. **(lack of time to use the resources that are available)** The other thing I guess is being, you know, what is on my desk here, a series of

adverse events. And I would think, you know I have two or three trials that generate enormous numbers of these MedRA reports. [right] So you know, that helps build the perception of the sort of side effects that are being experienced so. And there's a variety of resources, but do I go and look up every time I, you know something happens do I go back and look up you know in the investigator brochure probably not. [no]

M: And that's usually because of time constraints or [yes] any other reasons?

S08: Well and sometimes you know you've seen the same things happen in other patients [you don't really need to] so you don't really need to yeah.

M: Can you talk to me a little bit about these safety reports that you get, I, I've heard in other interviews that it's a bit of a, an issue just sort of the way the data is presented and.

S08: I mean they vary, some of them are, like this one, this is, these just came today, so these are from, from BMS or from Imclone, now these seem to be fairly detailed reports which is good and bad in a sense because if you're trying to look through 10 of them and you've got a couple of pages of detail. Like, 3, 4 pages, 4 pages of text, um, you know, it becomes difficult to you know, in a time constrained environment [right] to read that in a lot of detail. **(not enough time to pay attention to details)** So you are going to skim it and sometimes it's apparent because a lot of them are complicated patients, you know, people that come in and have multiple things go wrong and you know really that it's going to be very difficult to sort out. The whole issue of causality because there are multiple contributing factors. So sometimes you just look at it and think well yes it's possible you know, it's related. And what I find if there's a good succinct summary then you know, that's, that's very helpful and the reports are easy to look at. Mostly I find you know I tend, I agree with, with the conclusions they come to and sometimes um, I think there's a tendency to over report disease-

related symptoms as being related to the investigational agent by the invest, you know, to be reported by the investigator. **(tendency to over attribute protocol drug)** It's my sense in particularly in a series of things we are you know, reports that I got that related to a study of interferon and a drug called CCI-779 in renal cell cancer. And so in that setting there's a discrepancy between what the investigator feels and what the medical monitor feels. And then you have, because different companies will approach it differently and so then you have AstraZeneca with their reports. The company sort of reports basically they, they want to downplay um, these and so their stock standard line is that you know, such and such a side effect is not listed in the investigator brochure, the implication being well it can't be related. So you know they take the, so you've got to look at it with, it's somewhat helpful but somewhat tedious. **(Pressure from drug companies)**

M: Okay, so um, that, that would seem like a bit of a pressure then that you're getting from the sponsors. So do they actually write back to you in writing and say?

S08: No, cause what happens, they'll send us the report and then it's up to us to how we deal with it. I mean they have to be forwarded to the REB and the internal documentation that we do is more about sort of thinking for ourselves whether we want to make consent changes. Whether we see something which is happening you know, with um, severity or a frequency that would justify making a change to the consent form. And that doesn't happen very often, in part because you know, we tend to wait for, because periodically there will be an update to the investigator brochures and then they'll considered if the consents need to be updated. [right]

M: One of your concerns that you mentioned was that there was a tendency to over report disease related symptoms as being related. [mmm hmm] Why do you think that is?

S08: That, I mean, I don't want to sound like I'm being judgmental but there's, there's a propensity for that to happen in, from reports that come out, particularly out of Eastern Europe. [oh really, okay] So I think that there's geographic variation in, in the way in which things are attributed. And so I you know, particularly in Eastern Europe I'm more skeptical of, about the assessment of causality. But that's a very broad comment, that's not universal.

M: And do you think it's just a tendency to be overly cautious or not understanding the disease well?

S08: I don't know, I think that would be very difficult for me to answer [yeah, yeah] or hazard to guess at people's thought processes. [sure]

M: So what external pressures from third parties have you felt when assigning causality then?

S08: I don't think I felt any external pressure [no?] no.

M: You haven't felt um, you mentioned sort of AstraZeneca wanting to downplay.

S08: Well that's in terms of these reports, we [oh you mean, what you're referring to] [11:05] we receive, not necessarily the [at the bottom where they have their company comment?] yeah, not necessarily the ones that we generate. But not, I mean never been, I mean there have been times when we've had queries come back about um, about reports, but not. I mean I've never sort of had someone say we have to change something [okay] that would probably just make me dig my feet in I think. Um, I mean there's a difficulty because again, the way that um, the expectation for serious adverse event reporting seems to differ a little. [yeah] And for instance the [how so] well let's say you have someone that has diarrhea, mucositis and then becomes dehydrated. Sometimes in some places for some

companies you know the serious adverse event would be mucositis, diarrhea and dehydration. And other places and I guess the NCIC in particular, I mean our recent experience, is that they say well the drug doesn't cause dehydration, the diarrhea and the mucositis does. So you have primary adverse event and then you have secondary effects from that [right]. And then really only want the primary event reported as the serious adverse event and then what's secondary to that is covered in the description of the serious adverse event. **(Difficult to know what sponsors want report and how they want them reported)** So someone that gets um, you know, febrile neutropenia, who gets febrile neutropenia, sepsis, renal failure, pneumonia, and dies. I mean it may be that the only adverse, the only thing that might be considered the serious adverse event would be the febrile neutropenia. Um, so you know, it becomes a little confusing at times trying to figure out what should be on and I think the, um, the biggest problems that we've had in recent times in submitting SAEs has been you know, questions about what should be listed in terms, as the serious adverse events. [that's a bit of a challenge] It is and some of that is sort of developing a better understanding of what individual sponsors want or expect. But on the other hand maybe there should be you know, greater consistency.

M: You find that there is variation among the sponsors as to what it is that they want and expect.

S08: Yeah.

M: Now you mentioned that when you're thinking about causality you think of a number of things, you think about temporality, you think about whether the event is expected or not and you look at all the other possibilities and consider the drug. What do you consider to be the most important factor when you're assigning causality? Anything, any one thing in particular that sort of is most important?

S08: Is it a known effect of either the drug or other treatment as being received [yeah] would be I guess the most important thing.

M: Now I would just like to ask you to consider a scenario for me. [mmm] Let's say you're treating a 65-year-old female patient with a confirmed diagnosis of metastatic breast cancer. And she's in a Phase 1 clinical trial with a new investigational drug when she experiences a pulmonary embolism. How would you assign causality to the study drug if you knew that there was a 75% chance that it was related to the study drug and a 25% chance that it was related to other factors such as her disease progression, or chemotherapy or?

S08: I mean something like that I would say, I mean to say that there's a 75% chance that it's related to a study drug would indicate that there's a pre-existing um, you know, that it's already known that the drug causes thrombotic disease. And if that were the case then I would say it's probably related.

M: Okay, so your scale is certain, probable, possible or unlikely and you'd say probable [probable] okay.

S08: Because I mean it can be disease related as well. You're never going to be able to tease out a Phase 1 trial that it's definitely, definitely related. **(feels there are no concrete answers)**

M: And what about if those percentages were changed so that you knew there was a 50% chance it was related to the study drug and 50% chance that it was due to other factors? How would you grade causality then given the same scale?

S08: That's not a real life situation you're never going to know [no I know] so I mean I don't think I could answer what you're asking because you know, you're never going to have that degree of certainty about you know the likelihood. And you're left with a situation where you know that metastatic breast cancer is

associated with a risk of thrombotic disease. And if your investigational agent has been said to have an association as well then you know, it's, it's always going to be a, you know, a probably or possibly. If there's a clear knowledge that it causes thrombotic problems I'd probably say probably and if it was unclear I'd say possibly. Sorry to be difficult but you know there's no point in answering [yeah] a hypothetical question that's irrelevant.

M: Would you ever assign, can you give me an example of where you've ever assigned causality as unlikely [in any] yeah, sure, can you provide me with an example.

S08: Well someone that's on combination chemotherapy and a new agent where um, you know where you already have a high likelihood of getting neutropenia, you know, severe neutropenia then the patient gets grade 3 or 4 neutropenia then, on the combination then I would probably attribute it to the chemotherapy and say it's unlikely to the investigational drug. Unless there's already, you know, unless single agent studies of the investigational drug have been shown to cause neutropenia.

M: So in a case like that you'd feel fairly certain that it wasn't the study drug that it was the chemotherapy and that there was.

S08: Well I mean how do you be fairly certain about anything in a Phase 1 trial? I mean you're talking about a drug for which you have limited experience in humans by and large. The only way to know clearly whether the addition of your new agent to the chemotherapy causes an increased risk of, of side effects that are associated with chemotherapy is when you do a randomized comparison of chemotherapy alone versus chemotherapy plus new drug. Um, then you'll know what the true increased incidence is, for instance when you look at studies of Avastin and chemotherapy, I mean this is relevant to what we're doing currently in, with a trial in lung cancer with carboplatin, taxol and AZD2171. You know

that's a drug that blocks vascular endothelial growth factor. And you know, we've been faced with neutropenia and febrile neutropenia concerns and we've largely said that it's, you know it's been largely said that it's unrelated to the study drug. But on the other hand when you look at the studies of, of chemotherapy plus Avastin, a randomized trial, and Avastin is a similar class of drug, then the rate of neutropenia and febrile neutropenia is probably double that of chemotherapy alone. So there's some increased risk in related drugs and yet we're tending in Phase 1 to sort of say well okay it's probably not related. But the only way to know truly if the rates are increased is when we do a randomized comparison. So you've got to, there's a lot of imprecision in, in um, trying to tease out toxicities when they overlap with other drugs you're giving. I think to, to, you know, to suggest otherwise is um, is fraught with problems.

M: From your perspective then what would make assigning causality easier? Or do you just resolve yourself to the fact that it's an imprecise science.

S08: Imprecise science! **(key term)** I am not, I mean I guess to have definition, I mean more clearly defined sorts of definitions of the terminology would be most, would be the thing that would be most helpful. [which terminology?] You know, in terms of the causality terminology, so more clearly define what people mean by unlikely, possibly, probably, you know definitely related. And at least people are using the terminology you know, in a similar fashion. **(lack of consistent definitions)** You're always going to have difficulty in teasing out um, disease related symptoms. And you know, if you've got other treatments there you'll have difficulty in teasing out you know, concerns about overlapping toxicities.

M: So better defining the grade, the terms on the scale [yeah], anything else, what else would make it easier?

S08: Honestly, I don't think anything else would make it easier. You know, this is not, um, it's not something that there will be an epiphany and we'll say, oh this is

how to do it. [right] Because you know, of the nature of, of that, it's, it's evolution, it's knowledge in evolution, by definition. And because of the fact that you have limited experience in humans either of that drug alone or of that drug in combination. It may in fact be wrong to take away that um, that imprecision because the process needs to evolve really with each, maybe not with each patient but with each group of patients. I mean the, the knowledge of what the potential toxicities are evolves. [need to have room to evolve] **(imprecision leaves room to evolve)**

M: Okay, what I'd like to do now is just ask you to quickly read over these questions and cross out any that you think are not relevant to the Phase 1 oncology clinical setting.

S08: Phase 1, well there's no placebos in Phase 1. Just put a line through the whole one. [yeah sure just cross it right out]

M: Oh great, thanks, super. Is there anything here that you thought was missing? Anything that could have been added that wasn't there?

S08: I don't think so, I mean, well anything there that's not there is um, it's sort of there it says, I mean it's sort of there because it says are there alternative causes other than the drug that had, that could have caused the reaction. Um, I think you need to, to separate out you know, disease, you know, related symptoms and also the possibility of you know is this a Phase 1 trial of a new agent plus standard chemotherapy? Because if it's a new agent alone then it's easier to look at then if it's a new agent plus chemotherapy where you have to consider the expected toxicities of the, the chemotherapy or other therapy they received. [okay, good]

M: What do you think the implications are then, I just want to go back to, I think you bring up a really interesting point about it being an imprecise science and

that you know, you don't want to stifle that evolution of knowledge. On the other hand, what do you think the implications are of assigning causality poorly?

S08: Well I mean if you're assigning causality poorly I mean you start to get a profile of side effects, I mean, because the real issue in Phase 1 is does the drug go forward or not? And how, I'm not sure how often a drug ah, fails to proceed in development because of toxicity. More often you know, there are issues about ah, lack of efficacy or lack of perceived efficacy because again, it's more difficult to assess efficacy in that setting. **(efficacy is an issue)**

M: So, you don't really feel that there's huge implications in terms of the drug moving forward?

S08: Well I think that there are, I mean I think you know, if you start sort of labeling a drug as having you know x, y and z side effects and in fact they're in fact they're side effects related to the disease then you know, um that's a problem. But on the other hand does it, how does it limit development of the, the agents. I'm not certain, well I'm not less certain that it's going to limit development of the agent. **(not sure what the consequences of over attributing are)**

M: Okay, are there any other, like can you give me an example of a, of a drug that was sort of halted because of safety issues?

S08: Um, always when put on the spot, because a lot of these things are numerically identified at this point so they don't have um, [easy to remember names?] easy to remember names, but some of the um, there's at least one of the, the agents active against VEGF I can't think of which one it was, but not one that we were personally involved with. But there are some examples of some drugs in recent times that have just proved too difficult to administer. Whether the

anticipated toxicity of the drug, like the dose limiting toxicities occur at doses that are below what are thought to be biologically effective doses. [okay]

M: Now I guess I would just like to ask you a little bit about your experience as a clinical trials researcher. So which cancer(s) do you specialize in?

S08: Breast and lung. [lung and breast okay]

M: You have your MD obviously, what year did you get your MD?

S08: 198... it's on the wall isn't it, 1988.

M: 88 and you also have a PhD is that right? [yeah] and in what year?

S08: In 2000.

M: In 2000, and that was here at Mac right?

S08: No, that was in [Australia] Australia. Well I have a Masters in Clinical Epidemiology [okay and what year] that was in 199-- I graduated in 1998. The PhD was Health Services Research and it was all sort of based in Australia.

M: Any other education? When did you get your Medical Oncology License?

S08: 1995 [95]

M: And any other sort of research related education or?

S08: I don't think so, that's enough isn't it? [yeah, I think so] I mean I've got Canadian Certification but that's not, that didn't require additional training so it probably doesn't really count.

M: So what year did you become involved in clinical trials as researcher?

S08: In earnest when I arrived here, so 2000 is probably the simplest thing. I mean I was exposed to clinical trials all through my training. So really from 199, well from 1993 onwards. But as a primary researcher, 2000 onwards.

M: And what percentage of your work time would you say is devoted to clinical trials?

S08: That's a hard question isn't it [yeah] I mean do you count the time in, I think maybe 10%.

M: And of that 10% what percentage do you spend in Phase 1 and 2 trials?

S08: Maybe 30% of it.

M: And then the other 70% would be [would be in Phase 3] okay.

S08: You know, but it varies from time to time [yeah] I mean there's such a big fluctuation [yeah] depending on what's happening. [yeah, it's just an estimate]

M: And you've been a local PI [yeah] for a trial. Can you tell me about any education you've received specifically to do with assigning causality to adverse events?

S08: I did some causality, we did some causality things in the clin epi program, not necessarily causality associated with adverse events in phase one trials, but um, more looking at the issue of causality in general.

M: What did you learn about? Bradford Hills criteria? [yeah] Any other training specific to assigning causality in trials?

S08: No, just the protocols will come with, so some definitions about what they ah [what they expect] what they expect yeah. But nothing in terms of formal education, training, I'm not sure anything exists.

M: Do you think there's a need for something like that?

S08: I think there's a need for people to have some training in clinical trials, the conduct of clinical trials yeah. But I'm not sure limiting to just assigning causality in Phase 1 trials.

M: I think that's, those are all the questions that I have. [okay] Have you got any questions for me?

S08: No I don't think so.

M: If I have any additional questions later on is it alright if I come back.

S08: Sure that's fine.

Subject 09

M: So, I'll just explain what it is we are doing again. So even the most experienced clinicians find assigning causality to adverse events challenging and many groups, such as industry sponsors, clinical trial cooperative groups, research ethics boards, they all expect prompt and sensible causality assessments. But assigning causality isn't always that straightforward, and it can have large implications for both patient safety and new drug development. So we're interested in developing a tool to help clinicians efficiently and reliably assign causality during Phase 1 oncology clinical trials. And we feel that by better understanding your needs as a clinician we can make this tool more relevant to

you. So do you have any questions before we start? [no, it's clear] Good. So let's say one of your Phase 1 clinical trial patients has just experienced reporting, or she's just reported experiencing an adverse event. Can you just walk me through how that situation is handled?

S09: Well, I guess as I'm struggling with this in the Phase 1 trials, what's an adverse event. [okay] Because within the protocols they're not defined very well either. **(struggle to determine even what constitutes an adverse event)** So that you could get disease progression that's an adverse event which when you're coming into determining DLT's and moderate toxicity if you put you know, increasing shortness of breath could be related to disease. But when they say it's an adverse event that occurs on study, whether or not deemed related to the investigational agent you can potentially be putting disease progression [right] as an adverse event. So I think clearly defining what you mean by an adverse event upfront and what you mean by moderate and dose-limiting toxicity. But generally if somebody calls in with, say the call in with, you know, they've been short of breath, well they got the drug on Monday and today they're short of breath. So you go through clinically you know, what their symptoms are, like is it something that, if they've got plural effusions are they more short of breath? Is it something related to disease? have they got a fever? So you go through all those diagnostic type things first. And then from, based on that, you kind of algorithm out which way you're going to do. And it can be related to drug and you're always looking at the time, when their dose of drug was versus the onset of symptoms. [okay] If it's um, if it's listed as an expected in the IB, an expected toxicity in the investigational brochure um, versus disease under study, those I think are the three triggers. **(strong emphasis on IB and timing of an event)** The challenge with the Phase 1 studies when you're on these, doing these agents that are first in man you don't know. **(uncertain)** And a lot, I think we tend in practice to um, be over-cautious and possibly assess attribution if you've ruled out the other things and you have to say ah, possibly related to drug um, and then go from there. **(err on the side of caution when uncertain)** And it then it becomes, if

it's, I mean a bad enough toxicity where you stop the drug then you, if there's a re-challenge that happens and then you see if it re-occurs versus if it doesn't. [right] And, and, certainly even with, in the animal model, not all humans get the same side effects that animals do so [right] you know [so there's limitations to that] there's limitations [right]. That's okay and some of it too is, it's something too that you notice over time because you might not pick it up in one patient, but it's only as you think so and so had that and we didn't think it was related, well maybe it is. And I guess that's the limits of the phase one studies when you're dealing with a small number of patients. [yeah] And ah, I find it a challenge too when you're doing the accelerated titration design studies where they put one patient on per cohort [yeah] that you've only got one patient on that dose level. And we know that not all compounds work the same way in all disease type so it may not be effective in somebody with colon cancer but it may be toxic to someone with a lung malignancy. **(uncertainty- individual variation)**

M: Right, so that's a real challenge then when you don't have a large number of patients you can't

S09: So the first one may not have had a problem and you move on and you double the dose and that person may not, and then because a lot of them are open to patients with any malignancy, it's not geared to one specific disease site. So you're not putting the same patient with the same diagnosis on the study. [okay]

M: You mentioned that there needs to be better definitions of what is an adverse event, [mmm hmm] and I guess also better definitions of what is disease progression, right? [yeah, very much so] So you used the example of increasing shortness of breath, so that's sort of one of those ones that's difficult to tell whether it's [it is] an adverse event or a disease progression.

S09: I mean it's, because if you've got someone with say a lung with plural effusion or a metastatic breast patient that's got plural effusions or whatever and they worsen the disease. But a lot of them don't have biopsy that they're malignant effusions. And there's always the thing that's at the back of your mind that is, we always hope the compounds that we are developing target the malignant cells. But we know that they can target normal cells, so are they causing these patient's disease to take off? [right] and speed up the metastatic process with you know, and that's still back there with it. I've had 5 patients on and they've all progressed pretty quickly, was that the drug? [yeah, that's really difficult]

M: You mentioned that one of the resources that you use when assigning causality is the IB to check if the adverse event was an expected adverse event based on what you know [right] about the drug and in a Phase 1 study that's not too much. What other resources do you refer to then [for] when you're assigning causality?

S09: Well first of all it's usually, it's the PI's responsibility [so you refer to them] that's right. **(hierarchy)** Again it's the experience with the compound as you go along really, ah, if there's been similar compounds that are out there, um, that have been used. But in Phase 1 you're really, you're flying by the seat of your pants. **(interesting expression)** [flying by the seat of your pants?] Well you are I mean you don't know right, you don't know. [yeah] I mean they always start the Phase 1 studies at a tenth of a dose where they saw toxicity in the animal model, but that can be way too toxic right. [yeah] Then you know, I've got a study now where we're going backwards, the first dose was wrong so we're going backwards. [yeah, okay] It's mainly the IB and just what the patient had before they started study and if they don't have it before, if they don't have an adverse event before they start study then it's probably drug related. You have to, you have to say that, you know, you really do, so... [okay]

M: Are there any flowcharts, algorithms, decision trees, any sort of tools that you use to help you when you're assigning causality?

S09: No, no I'm not aware of any. [none that you use personally to help you out] No, again, I, I go with what the patient presented with at baseline [yeah] and what grade that was at baseline and then any change [yeah] is whether it's disease under study or drug. Other like you know the hot humid weather, everybody is short of breath and has swollen ankles. I think when we dictate we, well personally, if I'm, if we are leaning towards a few things that could have caused something, then we say could be related to this or this or drug and then we'll continue to monitor, And it's only over time you see a pattern or you don't. (**hard decision to make on the spot**) So you may assign causality in week three of possibly related but when you get to week seven something else may have come around and you think oh you know what? that back there wasn't. In hindsight it was like early disease progression or they were septic or something else will come out. [So it's ah, your knowledge sort of evolves over time] yeah, I mean you use your clinical assessment and um, and it's really process of elimination and if nothing else comes out. And then as you get more patients on then the pattern either develops or not. [okay] That's why I always tell patients to on a Phase 1 study that anything they feel like don't feel it's too trivial [yeah] if you usually have a bit of heartburn and now you have more heartburn, you need to let me know because it could be the drug. [yeah] Right, you know, just any change in your normal so that they know and it kind of [you can look at it] yeah, and it kind of, and I also pick on things that they might, or try to think of things that they might think are trivial or you know [yeah]. Like I usually say if you usually burp once a week and now you're burping every day. [laughter] it could be my drug and not you. [that's good you want them to pay attention to those things right?] Yeah.

M: So what do you consider to be the most important factor then when you're assigning causality? Is there any one thing that um?

S09: In terms of the drug [yeah] it's probably like the temporal relationship, is that what you mean? [sure like of all those things that you look for. You think the timing is the most?] the timing. **(significance of timing)** I mean if it comes on within an hour of drug or within a day of drug or you know, there definitely has to be something around that temporal relationship. And then you always see what happens when you stop the drug and if it goes away [yeah] you know. Sometimes, and again, it depends on the severity of the AE whether you rechallenge or not. And things often, I mean we don't know in terms, even with Phase 1 studies, some of them are, patients can continue on as long as they have stable or um, improving disease. So how long is too long? So they may have nothing in cycle 1 but then in cycle 4, so is it drug? [right] **(concern for patients)** You always look at, I mean there are always so many other confounding variables in this population, especially if their disease is starting to get a bit worse. They go on other medication, right which can impact, you don't know what these newer agents do with any of the other medications that are out there. There are just so many variables that can [yeah] affect, drug-drug interaction you know and drug-disease interaction, drug-foods. I always make a point of asking patients are they on any over the counter or complimentary therapies because they may not think, well I'm not taking any medication but they're on all these herbal or [yeah] just lots [lots of unknowns right?] **(so many unknowns)**

M: Now I was just wondering if you could consider a scenario for me. [mmm hmm] Let's say you're treating a 65-year-old female patient with a confirmed diagnosis of metastatic breast cancer. And she's in a Phase 1 clinical trial with a new investigational drug when she experiences a pulmonary embolism. How would you assign causality to the study drug if you knew that there was a 75% chance that it was related to the study drug and a 25% chance that it was related to other factors, say adjuvant treatment, disease progression, concomitant illness, concomitant meds. [hmm] Your scale is certain, probable, possible or unlikely.

S09: If there's a 75% chance then I would say possibly. [yeah, okay]

M: Now what if there was a 50% chance that the adverse event was due to the drug and 50% chance it was due to other factors?

S09: I would still say possibly [yeah] because I would say possibly drug and possibly disease under study. [yeah, okay] Again you would have to look at what else, I mean if they've just recently been on a trip to Australia and in a plane for [right] you always digging for what else they were and I mean cancer patients are more at risk for that.

M: And what if there was a 20% chance that the adverse event was due to the study drug and an 80% chance it was due to other factors? [and what was it possible] Certain, probable, possible or unlikely.

S09: Probably and unlikely, or possible. The first one should be probably when you're saying [oh the 75%] yeah, yeah, 20% I would still say possible.

M: So what do you think would be your lower threshold where you would say unlikely?

S09: I mean 20% is 1 out of 5, so I don't think that's unlikely and I don't think that's an unlikely thing for someone to get. I would think if it's a couple of percentage points then I would say unlikely. But when you're looking at 1 out of 5 I think that's pretty high. [yeah] So I wouldn't be comfortable saying in that situation that an AE is unlikely related. [so you said a couple of percent] Because even if we do um, we do our consents, um, when you're explaining risk ah, common is 20% or more [right, okay]. So and then rare, you know there's common, less common and rare and so if less common is less than 10% and rare is a couple of percents so [mmm hmm]. You know, if you were to say there's

a rare chance that you would get a PE so I'm thinking low, like 1 or 2%. [okay] So I, I do kind of think back to that, that comes from the IB as well and what we know but yeah. [okay] **(uncomfortable stating the AE is unlikely due to the protocol drug)**

M: Now given the choice would you prefer to grade causality as certain, probably, possible and unlikely or as a yes related to the study drug or no not related to the study drug?

S09: I wouldn't like yes or no. [you prefer the scale] Mmm hmm [why?] Just because you have that room to say that possibly, probably definitely and I think that helps overall than just saying yes or no. [mmm hmm, a bit of wiggle room] You need wiggle room and I would hate to say, if I only have yes or no then I'm probably going to pick yes more times than not. **(errs on the side of caution)** And I, I don't know in terms of the drug development, I mean I'm sure there's triggers for if you're getting people saying probably, probably, probably versus unlikely, what you're going to do right. [mmm hmm] So I wouldn't say yes and no. [the scale maybe is a little bit more informative]. I think it's more informative, it's more informative for me.

M: So what would you say are some of the problems or challenges when assigning causality?

S09: You don't know, in Phase 1 you don't know what's related to drug. In the later Phase trials you, you've got more data behind you but in the early Phase trials you don't. So that can be, I think that's a big challenge. [yeah]

M: Any other challenges? Even logistical challenges or anything?

S09: Well, I think you can overcall things that, and say that they're related when they're not. [mmm hmm] Um, and then that leads to for the drug companies to

sort out or, or you know, whoever the sponsor is in determining are these or are they not? And I think um, it would be beneficial at some point to follow through on the other end of things to see what it means when you're on that end. [what do you mean on the other end?] **(unknown consequences on the drug companies end- in terms of over attributing to the drug)** Like a CRO getting this information in and saying now, you know, oh well what does that mean, the word, how you take it and what did they do with it from that point. Because I mean we submit the information but what happens on that side, but I think. **(need for communication)**

M: So you think it would be nice to have some feedback and understand better how they?

S09: Yeah, I mean, say you look at a company like you know AZ or Pfizer, Aventis, Novartis, any of the ones that we deal with a lot is to be in there and see what happens, what happens when they get all these AE logs in and what does it mean and. And having the source documentation there to support everything that you're doing.

M: Yeah, no, it's an interesting question actually [good] that's.

S09: I think it would be beneficial for all of us maybe to spend a bit a time with them and see. Or even with the data management, I don't know what they do with the data management part of it. [yeah] And I think it would help us understand part of what we're doing too when you see how companies or CRO's try to collate the information we send to them. And then what it can do in terms of, you know analyzing the study or. [yeah]

M: What external influences or pressures have you felt from third parties when you're assigning causality?

S09: Um, well they come back and say well are you sure that's related? [mmm hmm] right [yeah] you know. No I'm not sure but I'm not willing to say it's not, you know.

M: Have you ever felt that you, have you ever been asked directly to change your causality assessment?

S09: Yep, we have.

M: How does that play out?

S09: Well, that's the investigator's call [yeah] yeah.

M: Any other pressures from third parties?

S09: Not that I can think of off the top of my head. I think all of us are very aware that the fact that the information we submit is what um, you know, can carry that compound further or not, you know. And how important that is and how important that is that we gather it properly as it is specified in the protocol to get all that information in. Even missing lab work can be important because you could miss someone's peak in liver function tests or whatever that could be a drug-related event.

M: Sort of the pressure to keep the drug development process moving I guess.

S09: Um, hmm, um, hmm. Yeah, very much so. And, and I think some of the pressures come around too is you know to put patients on study and sometimes that feels more, that's more the goal rather than the safety of the patient.

(pressure to progress study drug) I think we rely on the companies to monitor these studies and when they don't, especially the early phase studies, and when they don't there's a huge problem with that. I'm not perfect, and they're not either

but I think they then have the responsibility to monitor those studies and get those forms back into data management so they can make the proper queries that will probably, that could correct anything that you're not even aware of. [yeah, okay] **(mistakes are inevitable)**

M: From your perspective then what would make assigning causality easier?

S09: If you knew up front whether it was related or not. [laughter] [to know the impossible of course] To know if was or not. [if we only had a glance] Well I think that's, I don't know in the early phase studies if I knew how to make it easier, I don't know if there is a, you know. I think you look at the temporal relationship, that's the big thing in Phase 1, if it was around when they got the drug well, looks like a duck, walks like a duck, talks like a duck, it's probably a duck. [laughter] I don't know, I don't know how you would make it easier to assign causality. **(extremely difficult process)** You know like I say you go by the consent and the IB and, but I guess for everybody is to be aware of, you have to ask the questions and you have to dig. You can't just say to the patient well did you have any toxicities related to the drug?, because they don't know, they don't know what their looking for you know. [right] **(a lot of work involved-probing)** The same thing if you're looking for thinks like nail changes or something, well how do they know that they broke two nails last week that, that was just because they broke two nails or if that was because their nails are getting dry and brittle from the drug. [yeah] So you have, you're always thinking of you know everything. Like, I just had a lady on a study who's been on a Phase 1 study for nearly 3 years [wow], yeah, she has a really slow growing tumor. But she um, has noticed over the last probably six to nine months that her hair was getting thinner. Um, so is it drug related?, I don't know, it's not listed in the IB, it's not listed in the consent but nobody was on that drug either for nearly 3 years. So is it drug related?, you have to say possibly because [you just don't know] you don't know. So she said, so did the mice lose hair? she said, well we don't know because it was tested on nude mice. [laughter] You tested a chemo drug on nude mice?,

how could you?, how will you ever know if we'll lose hair?. She was just floored that the drug was tested on nude mice.

M: And the mice probably didn't get the drug for 3 years either. [that's right]

S09: So again, I don't know. Is that, people as they get older their hair gets thinner [yeah] is that a part of it? I don't know. But we have to say at this point in time that's it's possible related to drug long term, I don't know.

M: But it's good that you're recording it as that because it's hard to get that long-term data. [yes, that's right]

S09: And then if somebody else somewhere has that person and has another person on maybe they'll see the same thing I don't know. **(others rely on reporting)**

M: So what I'd like you to do now is to read over the following questions and cross out any that you don't feel are relevant to the Phase 1 oncology clinical trials setting.

S09: What do you mean by conclusive report, do you mean by an AE or SAE, what do you mean?

M: Um, well I didn't actually write these questions. [oh okay] Um, these, this was a tool developed by a researcher named Naranjo [mmm hmm] to help clinicians assign causality [mmm hmm] and so I guess it's however you would interpret it. So previous conclusive reports would be yeah I guess

S09: Like from an SAE whether they felt there was some, a definite relationship? [I guess yeah] Okay, I wouldn't cross out any.

M: You wouldn't cross out any? okay. So now then would you mind just ranking them in order of importance, so 1 would be least important, 10 would be most important. [laughter]

S09: Some of this you wouldn't have when assigning causality [what is it] like I wouldn't know there are conclusive reports and I might not know the pharmacokinetic [number 7 if the drug was detected in the blood?] mmm hmm. [okay] See we, when I'm assessing causality it's kind of on the information I have at the time and you know you may not, you may not know this.

M: And what about the previous conclusive reports, would, you wouldn't know that?

S09: No, you might not, you might not have them. [okay]

M: I guess it comes back to how you interpret that right [yes] because you could just say oh well that means if it's in the IB in which case you might, you would have that. [right] But, you're thinking in terms of the safety letters? [mmm hmm you might not have it] okay, fair enough. [So] It's good to keep in mind yeah. There are no right or wrong answers it's sort of a general.

S09: They're all pretty well, like all of these I would, I would think they're pretty well part of

M: You can assign them the same number, they don't have to have all different numbers if you think they're equally important.

S09: I ranked them but [ok good] I wouldn't, I think a lot of them could be the same. I would think this and these are like really important. [yeah, okay] And if there pharmacokinetic data is right up there that will really [that helps] oh yeah [if it's available] if it's available. Because actually usually when we see some toxicity

on there then we'll ask for the PK samples to be shipped. And then we'll look at them to see what, but then when I'm doing that note that day in clinic do I have that?, no. [right, right] And they want something assigned at that point in time, so that's why I think you overcall them because you have to, again for the safety of the patient be, be over cautious and say possibly or probably related. **(err on the side of caution)** [yeah] Although you may modify it at that point in time and I think that, maybe that's part of the time pressures is that you have to make a, an assessment call on that day that you see the patient with the, the data that you have at hand. Not looking into it you know down the line. [okay, good that's great]

M: Then lastly [mmm hmm] I would just like to ask you some questions about your experience as a clinical trials researcher. So in which cancers do you specialize?

S096: Breast.

M: Now you have your, do you have a Bachelors then [yeah] in nursing. And when did you receive that?

S09: 99.

M: And do you have a Masters? [no] When did you receive your RN license?

S09: 79.

M: Do you have a diploma in nursing as well? [yeah] yeah and when did you get that?

S09: Well ah 79.

M: And is there, are you a nurse practitioner? [no] no. Do you have any other sort of?

S09: Certification in Oncology, yeah [is that the CANO?] yeah.

M: And what year did you get that?

S09: Oh, 2002/2003, 2003 I think.

M: And what year did you become involved in clinical trials as a researcher?

S09: Here? [well how long have you being doing] 95. [95 okay]

M: So what percentage of your work time would you say is devoted to clinical trials then? 100%?

S09: Well yeah.

M: And then what percent of that is devoted to Phase 1 or 2 trials?

S09: Well I was going to say because up here I do breast and I backup neuro but because I do Phase 1, I do them all. [oh okay] So I don't consider myself an expert in all of them but I deal with a lot of [different types of cancers] yeah, yeah. So what was your other question, sorry.

M: What percentage of your time is devoted to working on Phase 1 or 2 trials?

S09: Right now, 80.

M: 80% and then the other 20% would be Phase 3?

S09: Well actually, some of my breasts are Phase 2, 80 yeah [yeah] yeah.

M: And then is the rest of your time spent on Phase 3?

S09: Yeah [yeah, okay]

M: Now, lastly I'd just like to ask you a little bit about the education that you've have received [mmm hmm] with regards to assigning causality. So can you tell me about any training that you've received specifically with respect to that? [with respect to causality?] Yeah, assigning causality.

S09: Um, I guess it would just be at the start up of each trial, in terms of a formal course related to causality? [mmm hmm] I mean, they have sessions on it at the NCIC Spring meeting and you know different conferences that you go to. You know like the San Antonio Breast Cancer but I mean, that's probably about it. I think that's probably a huge gap [yeah] mmm hmm. **(believes more training is need)**

M: So at each study start you receive some training?

S09: They go over what, they go over adverse events and what they are [and that's from the sponsor?] yeah. [so what an adverse event is] What an adverse event is, how they get logged in the form, you know, assigning grade, you know, even in terms of causality, I don't even really know that they go over that much in causality, it's just the fact that [they don't go over it too much?] they really don't, the fact that it's more if it occurred on study or if it's something new you know, then it's an, call it an adverse event. But do they say assigning causality, it's actually pretty poorly defined. Because I think even as you were looking for it the other day, it's not even in there, over [definitions of the terms in the scale?] mmm hmm [yeah]. So I think that's something that industry needs to, well not industry, it wouldn't be industry, but all of us need to [come to some sort of consensus]

consensus on yeah. How do you assign not possibly or probably [yeah what do those terms mean] yeah. **(feels there is a need for consistency)**

M: So what additional education about assigning causality do you feel needs to be made available to clinicians? So we just talked about the definitions [mmm hmm] on the scale.

S09: And I guess what does it mean to the sponsor? When they're, when they want, when they ask for unlikely, possibly, probably, what is the criteria that they are [yeah] wanting you to use to assign, to make that decision? What are they asking you to make that decision based on? **(more communication needed with sponsor)**

M: So I think that's all the questions that I have for you, do you have any for me. [no] Well thank you for the time you spent with me today.

Subject 10

M: So, what I'll do is I'll start by explaining exactly what it is we are doing [mmm hmm]. We're looking at the way investigators, clinicians assign causality to adverse events in Phase 1 oncology clinical trials. And even the most experienced clinicians find assigning causality to adverse events challenging. But many groups, such as industry sponsors, clinical trial cooperative groups, research ethics boards, they all expect prompt and sensible causality assessments. But I'm sure as you know it's not always straightforward and if done poorly can have large implications. So we're interested in developing a tool to help clinicians efficiently and reliably assign causality during Phase 1 oncology clinical trials. And we feel that by better understanding your needs as a clinician we can make our tool more relevant to you. Do you have any questions before we begin? [no] Okay, so let's say one of your Phase 1 clinical trial patients experiences an adverse event. Can you just walk me through how that process is handled?

S10: So normally they would be brought into clinic for an actual assessment, so a history and physical, so detailed questions of what the adverse event is, when did it occur, what are the specifics of the event in terms of the severity. What treatments if any have already been tried by the patient and if they have seen their family doctor for example. So what sorts of interventions have already taken place for the ah, adverse event. So just a, basically a thorough history in terms of the actual symptoms that they're having and the treatment to date. And then a focused physical examination related to what the ah, adverse event is and um, so that's what we would do in terms of seeing the patient in the clinic. And do you want it detailed right to the end?

M: And then I guess you would have to assign causality at some point.

S10: Yeah, so I would want to do some investigations, depending on what the adverse event is. And then depending on the ah, findings, assign the causality. [okay]

M: And how do you go about assigning causality?

S10: So I look to see what the adverse event is, is it something that is known. I'm assuming this was a drug trial, yeah, is it something that is expected from as a known side effect of the treatment. **(assumes its a result of the drug)** Um, temporal relationship to, to the drug.

M: Now can you explain what you mean when you say a temporal relationship?

S10: When did it occur, so if it occurred before they even got the drug well then that 's not going to be related to the, to the drug. However if it occurred a few hours after and it's happened repeatedly after taking the drug then you can see that it's associated with a certain time element related to taking that medication and that sort of temporal association makes you more likely to suspect that, that's

related to the, to the medication. **(use of temporal association)** So those are the two big things in terms of the, assigning causality. And then just looking to see how severe it is [okay] and what intervention needs to take place from our end to deal with that. You know, stopping the drug or supportive treatments.

M: And so what are the resources you refer to when you're assigning causality?

S10: I'll be honest and say I don't really have any [really]. I don't have any tools that I use, I just know from taking part in the studies that you ah, look at the key features that have already been mentioned in terms of the relationship to the study drug, timing, reproducibility, that sort of thing. So it's more on a, just based on the experience of taking part in the study and the hunch factor. I don't actually have a tool that I use, so I think something like this would be very handy. [okay] **(uses own experience, but feels a tool would be helpful)**

M: When you're determining the expectedness of the adverse event though [mmm hmm] you'd probably have to... How would you determine that?

S10: Well it depends on the pre-clinical information, what we know already from um, earlier studies. From patient volunteers who have been on the study, who have been on the drug, so if you know that rash has been seen in patients before this, this study then that's something you can expect. Or from other agents that are similar, if you're testing drug x and drug y is similar to it and it's been reported that it has a rash for example then it's not unexpected. Knowing the mechanism of action of the drug, you can postulate that there are certain expected side effects if you have a drug that affects your blood vessels and bleeding is something that you could logically expect would be an adverse event. [mmm hmm] So ah, just based on the biological plausibility factor as well in terms of assigning the, the adverse events.

M: Do you refer to the IB at all?

S10: Yeah, yeah that would be available.

M: What general guidelines do you follow when you're assigning causality, are there any sort of rules of thumb that you, you know, you said you sort of go by your

S10: You can look at it in terms of unexpected, probable, possible, the usual five, unrelated and what not.

M: And do you personally have any kind of [how do I assign?] yeah.

S10: Not that I can admit to quite honestly. It's basically just that you know, if it is something that's recorded in the IB or in previous studies then yes we would put that as expected or probable. Otherwise if there's any kind of concerns, then possible, you know if they got it, if they got the adverse event before they even got the medication or there doesn't seem to be a temporal relationship, then unexpected.

M: Now of all those things that you mentioned you consider when you're assigning causality, what do you feel is sort of the most important factor?

S10: To put a weight on it, I think more the biological plausibility, is there a mechanism that you can see as to why you would have that reaction? It makes scientific sense that this could be an adverse event related to that particular drug. And the temporal association, the timing of the reaction. Often sometimes with people, you do a little bit of a drug challenge where you see if it comes again. Like if they have the reaction and it's a drug that they're getting daily, well you stop it for a little while and see if the reaction goes away and then you re-challenge and if after a couple weeks it comes back, well then you've got your temporal association right there, relationship there. [okay]

M: I just wanted to ask you now if you could consider a scenario for me. So let's say you're treating a 65-year-old female patient with a confirmed diagnosis of metastatic breast cancer. And she's in a Phase 1 clinical trial with a new investigational drug and she experiences a pulmonary embolism. [mmm hmm] How would you assign causality to the study drug if you knew that there was a 75% chance that it was due to the study drug and a 25% chance that it was due to other factors, say disease progression, concomitant illness, [mmm hmm] concomitant meds and the scale is certain, probable, possible or unlikely?

S10: I would say probable, just based on the 75% likelihood, but with her underlying malignancy she's at risk for developing a DVT, pulmonary embolism regardless I wouldn't say certain based on that feature. [okay]

M: And what if there was a 50% chance that the adverse event was due to the study drug and a 50% chance it was due to other factors, how would you assign it then? [so with certain, probable] possible or unlikely.

S10: I think I would still say probable in that situation.

M: And what if it was a 20% chance that the adverse event was due to the study drug and an 80% chance it was due to other factors?

S10: Possible. [possible, yeah]

M: And you know, what sort of, I know that you never really get these percentages in real life, it's very hypothetical but what would sort of be your threshold for unlikely? Can you think of [in terms of percentage?] yeah.

S10: 10 [10 or less yeah] mmm hmm.

M: Just to get an idea of where people are coming from, it's purely hypothetical.

M: And given the choice would you prefer to grade causality on a scale like I just gave you [mmm hmm] or a yes related to the study drug or no not related to the study drug?

S10: I like the scale because yes/no is pretty black and white and often there are many scenarios where you're just not sure.

M: What would you say are some of the implications of assigning causality poorly?

S10: I think the biggest implication would be that if a drug gets attributed to have a set of adverse events that are quite serious then that may preclude further study of that drug, that might stop the trial. And if you're looking at a dose escalation study where you're escalating to your next dose based on the tolerated dose, you're now saying that there's some side effects. Well you might not go to the next dose level, or you're recruiting more patients to that particular cohort level so subjecting more people to the drug than may be necessary in a clinical trial. So the issue of not, of a potentially very good drug not being taken further because of the concerns of the adverse events, that's going one way. And the other way if you don't attribute the causality, a potentially dangerous drug could come to market without the proper, or with concerns about adverse events.
(consequences of attributing causality poorly)

M: Have you every seen anything like this before or can you give me an example of anything?

S10: Well I mean you can think about the whole issue of the Cox 2 inhibitors in terms of the cardiac events and the whole issue of attributing causality perhaps if, in the earlier studies that was something that was strictly monitored it might not

have gotten to the point where Vioxx had to be pulled off the market for example. A lot of those events only came to light once the drugs were well into the community. So that would be the big one that comes to mind.

M: And what about personally within your area of oncology, have you every witnessed anything like that or ... not, not like the Cox 2's but just you know maybe experienced a trial that was halted?

S10: Well I can think of the ah, one particular study ah, letrozole plus CCI779, one of our Wyeth industry studies where it was stopped because of lack of efficacy, concerns of some adverse events I believe. It's the only one, recent one, that comes to mind.

M: And were there causality issues around that?

S10: Not that I know of, I wasn't ah, I was on maternity leave when that study got stopped so I'm not sure of the circumstances around it. Kind of heard about it second hand when I came back to work and said I think I have a patient for it and learned that it was closed. [oh, right, okay]

M: What would you say are some of the challenges when assigning causality?

S10: I think the biggest thing is determining the actual act of assigning causality. **(big statement)** You're never really 100% certain so the whole issue of probable, possible, you know, I think we kind of have an idea of which way it swings, it 's just the degree of certainty. [mmm hmm] Whether you think it is attributable to the medication at hand.

M: So it's difficult to even know what your degree of certainty is? [mmm hmm]

S10: Often these patients are just, have such complicated histories, you know, they're prone to other medical problems. Particularly I find the difficulty is with the thrombotic events is a big one in terms of, is that because of their underlying cancer where they're already prone to clotting issues as opposed to the medication. And how much is the medication increasing their already baseline risk of having those kinds of events? [yeah, yeah, okay] Older patients with cardiac events, the same sort of thing, if you've got someone with diabetes and high blood pressure and other cardiac risk factors, the same issue of how much is the medication increasing their baseline risk for a coronary event.

M: What do you think might help in that situation?

S10: Boy wish I knew [tough question] yeah. I mean certainly for the coronary events if you had an assessment perhaps by a cardiologist you could say that this is their baseline risk of a cardiac event. And if you knew that beforehand that would certainly help with, with that side of things. Certainly from the cardiac point of view I could see that would be helpful but for most events I don't know that you could get a similar assessment and say you know this person's risk, baseline risk is x% and the drug will increase it by 20% or 30%.

M: What are your concerns about how clinicians are currently assigning causality?

S10: Well I think just the fact that there, there isn't a systematic way to do it, that it often is based on hunches and feelings as opposed to a rigorous method or measurement tool.

M: Can you give me an example of when something you know, when you assign causality based on a hunch or a feeling?

S10: Well I can think of one where the person had a lot of diarrhea after their chemotherapy, but mind you they had had quite extensive bowel surgery so they'd had some difficulty with diarrhea before they even came on the study. Yet diarrhea is a known side effect of the medication that they were on so you know, how much was it increased from their baseline? So that was more based on a hunch in that situation. [yeah]

M: And how did you assign causality in that case?

S10: Well probable, because of the, the knowledge that that particular drug, diarrhea was something that was seen.

M: And what external influences or pressures from third parties have you felt when assigning causality?

S10: Well if you're involved in industry studies then certainly there's some pressure from, not so much for assigning causality but continuing. So if you've had someone who has had an adverse event and you want to dose reduce them or hold off treatment for a little while sometimes there is that pressure to continue with the study. **(feels pressure to move drug forward)** So in that sense you could think well maybe if you had assigned them a possible as opposed to a probable relationship then you could, you could be pushed to continue with the study. But you always have to keep the patient's safety in mind [right] at the end of the day so, so that's what you go by. **(however, patient safety is most important)**

M: So if the patient, if the SAE was downgraded from a probable to a possible [mmm hmmm] that would mean the difference between the patient continuing on or

S10: Continuing on the study or possibly coming off the study, that again would depend on the side effect, and the severity of it, depending whether it's treated or resolved, the outcome of the, the adverse event. But I must admit I really haven't had that much pressure in terms of treating the patient. It always comes down to the patient's safety and that's what you go by. [okay]

M: From your perspective what would make assigning causality easier? You said you know, maybe a tool would help [mmm hmm] that would sort of make it a bit more systematic.

S10: I think more information about, and it's difficult because these are Phase 1 studies so this is the first time you are testing it in patient, patients. Better pre-clinical data in terms of the data of these mechanisms of these medications so that you could, the whole biological mechanism of action so that you can think that well maybe this is something that makes sense and foreseeably cause some of these adverse events. That certainly would be helpful for assigning causality. [yeah] Does that mean more pre-clinical studies or better assays or information in terms of the, the way these drugs work? Because often times we really don't know, we think it's one particular way and then these other side effects come to light. And you're wondering well, that doesn't make sense, why would they get this side effect and then you do some more bench top work and find out that well okay, it may also be affecting this pathway and so that makes sense in terms of the side effects.

M: Now I would just like to ask you if you wouldn't mind completing a little exercise for me. So if you could just read over these questions and cross out any that you think aren't applicable to the Phase 1 oncology clinical trial setting.

S10: They're all pretty relevant.

M: Then, now if you could just rank them from least important to most important from your perspective, there's no right or wrong answer.

S10: Should I just put the numbers right here?

M: Yeah, if you don't mind, so least important is 1 and most important would be 10 and you can just kind of arrange them in order. [so most important is 10?]

Yeah. Okay awesome. So number 10, question number 10 you ranked the highest as being the most important. So was the adverse event confirmed by any objective evidence, what, what did you interpret objective evidence to mean there?

S10: Well actually any physical findings for example.

M: So could you give me an example of something like that? [like a rash] okay, so if you actually saw the rash or something [mmm hmm] okay, good. And then the lowest one you ranked was did the reaction reappear when a placebo was given [mmm hmm], why did you rank that one lowest?

S10: Thinking that sometimes you can have a reaction, I mean because they have a placebo for example, let's stick with the rash scenario, you can get a rash from two completely different drugs, it doesn't matter that, I mean you get a reaction to drug x and a reaction to drug y. The reaction to drug y doesn't necessarily have anything to do with the other. So for example they could be, in that example they could be someone who is prone to rashes or that drug brought it out so. It was more that in the grand scheme in all these points it seemed to be the least important to me in terms of the causality. [okay, great]

M: And then are there alternative causes (other than the drug) that could on their own have cause the reaction?, that wasn't too important either.

S10: Again, important but just out of all the others felt it to be lower. [okay, good, great, thanks]

M: This is actually a tool that was developed by a researcher named Naranjo. [mmm hmm] And the thought is that maybe we might modify this [mmm hmm that's very good] to make it more relevant to the oncology setting. Were there any questions here that you felt were missing, there should have been something here that wasn't. Something that you think about when you're assigning causality that you didn't see there.

S10: Nothing that comes to mind off hand, it's pretty thorough.

M: Then I just need to ask you a little bit about your experience as a clinical trials researcher. [mmm hmm] So in which cancers do you specialize?

S10: Breast and GI [breast and GI]

M: So you have your MD [mmm hmm] what year did you get that?

S10: 1996[1996]

M: And when did you receive your medical oncology license?

S10: Um, 2000, sorry 2001 [2001]

M: And do you have any other, do you have a Master's in ClinEpi [yes I do] yeah, what year did you get that?

S10: 2004 [was that here at Mac?] Yeah.

M: And then any other sort of education that you have to do with clinical trials?

S10: No. [no]

M: And what year did you become involved as a researcher in clinical trials?

S10: It would be about 2001 on my own?, because part of my fellowship I was doing research so would I include that [oh okay] as well? [sure yeah] so that would be about 2001.

M: And then overall what percentage of your work time would you say is devoted to clinical trials then?

S10: About 30%.

M: And then of that, what percent is devoted to Phase 1 and Phase 2 trials?

S10: Um, Phase 1 and Phase 2, about half.

M: Okay, so 15% and then the other 15% would be for Phase 3? [yeah]

M: And have you been, you've been a local PI before [mmm hmm] on a trial? [yeah]

M: And now, lastly I'd like to ask a little bit about the education that you've have received specifically to do with assigning causality. [mmm hmm] So can you tell me about any training that you've received specifically for assigning causality for adverse events?

S10: Just basically the investigator meetings related to some of the studies [okay] There was a little bit of a workshop attached to the meeting in terms of the basic science background of the drug, the mechanism of action, what the expected

side effects are from other studies of the agents. And going through the causality forms. Quite limited. [mmm hmm, okay] **(feels training was limited)**

M: What additional education about assigning causality do you feel needs to be made available to clinicians?

S10: I think having a workshop that's independent of any particular study or study sponsor, just in general on oncology drugs and assigning causality would be, would be useful.

M: And do you think that would be good for just clinicians or all [anyone involved in conducting clinical trials] clinical nurses too [trials yeah]. What would be covered there then in that sort of a workshop, what would be helpful.

S10: The key things to look for in terms of assigning causality that's ah, what are some causality tools, those are the two big things. [okay great]

M: Well I think those are all the questions that I have, I really appreciate the time that you've taken to speak with me today. And um, is there anybody, we're also interviewing clinical trials nurses to so, is there anyone that you recommend we speak to?

S10: In terms of the Phase 1 studies [yeah] I know ST is involved in a lot of my Phase 1 studies or AI and then any of the Phase 1 trial nurses, you can get that list from B in terms of [yeah, I think I have] probably have them. [yeah, I've got S and I've got A so that's good, thank you]

Subject 11

S11: I find it is a little bit tough sometimes just because, yeah, I mean that's where all my training is and I can't use that so I do find that a bit frustrating.

M: So you've got that nursing background but [exactly] in this model of care you're not able to.

S11: No and which ah, I have since found out and I am very, still relatively new to the department, I've been here for just 10 months. [yeah] Um, and since I've met so many other people from different centers at meetings that I've gone to, our, like you said, our model is much different [yeah] than other centers. We don't have "clinical trial nurses" that just work in clinical trials [right] and just do, except of course, for myself. So in that department it's much different, when we take on Phase I studies and things of that nature we have to find the most appropriate hands-on nurse down in the clinic who tends to be Dr. B's primary nurse, his name is xxx xxx. So he has agreed to work with her and myself on the early phase studies. [okay] So again, it's a little bit different, he is not a clinical trials nurse he has just agreed to work with us when there are trials that need somebody to dedicate essentially most of their time to them. [oh, okay] So it's a little bit tricky, it's a little bit tricky and there are a lot of hands in the pot but a lot of the times, just because we have to coordinate everything together instead of me just performing those functions. [right] Which I am qualified to do but can't. It's just a bit tough, it's a little bit tough in that way [okay] yeah.

M: So can you just explain to me then what happens or how you handle, just walk me through the situation of one of your Phase I clinical trial patients [okay] who has just reported experiencing an adverse event. How, how does that work in your model?

S11: Just so you know, the one Phase I study that we've opened since I've actually been here, we haven't been successful at accruing anyone. [okay] Um, but it would be very similar to any of the other trials. I'm currently doing a couple of Phase II, and I just got done an IND trial. So essentially the person would report back to me and probably also D and Dr B as well, three different times. Typically I like to see the patient first so that they, sorry, D would actually see the

patient and initially bring them into the clinic or doing what he would be doing with them. I would see them next and then the physician would see them last. Um, after the time we had, each person had seen the patient, when we come back out into the clinic area, the physician and I as well as the nurse would discuss what the patient had told us. And at that point it would be, usually at that point it would be determined, do we concur or does the physician think that it is attributed to study drug or not. So it's usually right after we see the patient we would discuss it and make the causality at that time [right, okay] so.

M: And so what are the factors that you're considering when you're making that assessment?

S11: Baseline, um, typically, so what they've reported at baseline or their previous medical history. Um, anything that they had been experiencing up to that time as well as have we been seeing um, I mean depending of course, on what cycle they're in, or how many treatments they've received, is this something brand new that we can actually say it seems to be coinciding with the infusion or injection of drug. Is this something that each week when they get that infusion it's been getting worse, it's been getting better. Um, good example, like I said, I just finished an IND study and we had a gentleman, liver cancer was his primary, um, never had problems with rashes, itchiness, that sort of thing, and day one after his first infusion he developed a rash desquamation. Um, and each time it actually, each time he got his infusion every three weeks, it again would reappear, um, actually the severity would increase each time. Um, so at first our process, in that instance, at first we didn't know, we thought possibly but it was unknown. The second time it was, well you know, now it's a possibly we've seen it twice now, and it seems to be getting worse with each infusion and essentially it went up to, he ended up getting only four infusions but at that point it was definitely related because he hadn't, he didn't experience it in-between. It was just the first four days following the infusion, it would go away and again once he got the infusion, four days following he would get it again. Um, so a lot of timeline

things, a lot of timeline things and checking back in their medical history to see is this something they've experienced before or is it brand new with the infusion of the investigational drug? [okay, that's great] **(timing of AEs plays a crucial role)**

M: Are there any other things you consider when you're assigning causality?

S11: Again, unfortunately it's not really my department, ah, um, the IB of course, you know, what's expected to be related to these drugs. Um, if nothing is mentioned I do, and again this is something that separates me a little bit from my coworkers in just, I will also check out the class of drug. Are there any sister drugs or closely related drugs that produce similar or that are expected toxicities for that? **(feels she goes beyond coworkers, but looking into the class of agent)**

M: And where do you go to look that up?

S11: CPS, I use a lot of, also our Cancer Care Ontario Handbook, I search MEDLINE Plus, there are a couple of cancer websites that I use also. Um, I don't know the name of them off hand. But in terms of chemical make up I will look into that too. Of course I don't get to make that decision but I make those suggestions to the PI, is this a possibility that it could be related to the drug? [okay, great]

M: And then um, do you know of any tools that are available to help in assigning causality? Have you every used any sort of a decision tree or an algorithm or [no] something like that? No. [no] Do you think that would be useful?

S11: I do think that would be useful um. **(feels a tool would be useful)**

M: When wouldn't it be useful?

S11: Um, it's hard to say, I mean everybody is so very individual right. So even though it's nice to have algorithms and schemas, that sort of thing um, everyone is going to react to everything differently. **(hard to compensate for individual variation within a tool)** And of course it depends on the medications they're already taking, their con-meds and pre-existing conditions. Um, so I can't really think of a specific, a specific time that it wouldn't be appropriate, but of course it's going to be, you can't lump everything into one big catchment area, it would have to be individual for each patient, unfortunately, which [mmm hmm] I'm not sure would be feasible. [right] **(feels tool needs to be focused around the individuality of each patient)**

M: What do you feel are some of the major challenges to assigning causality?

S11: Um, I mean the chemical makeup of the drugs and I mean it's not necessarily, I mean I'm certainly not claiming to know every drug off hand and what, even common side effects, things like that. I think being just that little bit removed, my entire department, not just myself but my co-workers also in that um, again I'm the only one with oncology training per se. Um, but even myself it's, it's not always possible to know exactly each drug and all the drugs and all the new drugs that are coming out. Every year there are new regimens as well as anti-emetic regimens that go with specific chemotherapy regimens. Um, yeah, so again everything is, is so highly variable even you know, what treatment did you get before in combination with this one? A lot of the times I find it's hard and I don't think it's an on purpose thing from patients, but I don't necessarily think that we do get every single bit of information all the time. [yeah] I think different things are reported to different people, depending on your position, whether that be chemo nurse, clinical trials nurse or the physician.

M: So how does that differ, can you just give me an example of a time when that's happened?

S11: It happens quite a bit you know where the patients will tell us in clinical trials that they feel great, a little bit of pain here and there, that's sort of thing. And then you read the physician note or you discuss with the physician after their meeting with the patient and they've been having nausea, swelling, you know, intermittent bouts of cough, that sort of thing. So I think it definitely depends, again, very individual, depends on the patient, depends on your personality, what you're asking. If you're asking the appropriate questions or not, I think that that makes a big, a big difference too.

M: So getting sort of consistent and reliable information from patients [yes] is a bit of a challenge [yes] in assigning causality.

S11: I think so, I think so, I would like to think that that's just not here, that, that would be everywhere. [you're not the first person to say that, don't worry] Um, even working on the in-patient floor, it's very different, even nurse-to-nurse, even minute-to-minute. Um, you know, one person might go on break and lo and behold you know, something new pops up that you know the actual attending nurse had no idea about. Um, I think, personally I think rapport is one of the, the biggest things and whichever, whichever clinician that may be. I don't know how you would actually streamline that into making sure that everybody is getting all the same bits of information. [mmm hmm, a challenge] I don't know that, that would be possible, [yeah] human nature, right so. [right]

M: Any other challenges that you can think of when it comes to assigning causality?

S11: Well I mean I think it's tough too when the drugs are so new and there's not a whole lot of things known about them. I think it's very, very different what a drug has been showing in the lab or with test animals as opposed to humans. Um, I think even site to site things are very, very different.

M: How so?

S11: I think, again I think that processes, process is pretty huge in things. So actually your centre and our centre I think are very, very different in that, I believe, and correct me if I'm wrong, that nurses in your chemotherapy centre are trained to put in pic lines and things like that. [mmm hmm] Here that's not done, it's actually done in interventional radiology, it's a surgical procedure, it all goes through there. [okay] So I know at the Juravinski Centre they're showing some sort of side effects and again we haven't put any patients on. Some side effects I'm not sure how that's being attributed to the study drug but I have to wonder if certain processes maybe show different things.

M: So you're wondering because the nurses can put in pic lines [that's just the only example I can] yeah, that's a good one [yeah] but could that somehow explain some things. [exactly]

S11: All, I know very little about what's actually going on at your centre only because, obviously we are so far apart and your girls are so busy there working because they have quite a few patients on study. Um, but I do know that quite a number of people have had pic (**PICC?**) line infections and that sort of thing and have had to come off study drug. And I would be very interested to see if it's the same thing here. Um, so again I don't know how causality has been, like how it's been determined or what it has been determined to be in, at Juravinski. But I would really like to know and I'm interested to see what happens here. And do those, they're underlying processes that we might not be considering, but do those things, whether it be procedures done by intervention or even past, past procedures, does that have an effect on how patients react to the drugs and do, are we taking that into consideration when we're assessing causality? [yeah, mmm hmm] Because I think every centre is so very different and I think we all don't really realize it until we visit another site. [that's a real challenge]

M: So what do you think would help in assigning causality, what sort of things do you think would help? [yeah] Let's just talk about the differences in the processes between sites.

S11: Um, for me it's been nice, again, I haven't had any patients on our Phase I study but for me it is nice that A takes it upon herself to call me and let's me know what's happening with her patients. And I know again, that's not very feasible when you're running studies that are multi-centre and quite multi-centre, 10 or more. I mean it might not be possible to correspond on a regular basis.

M: Are you referring to the clinical trials nurse at the JCC? [yeah] Axxx [yes, yeah]

S11: So I mean, we, there are only three sites that are participating. I know that they have been having teleconferences every Thursday morning I believe, um, where they discuss things. A she has [announcement 14:14] called me and we've discussed what's been going on with her patients, do you have any hints or tips I can tell my patients? For me that's great in terms of well maybe we should be watching out for these certain things. Again, I didn't ask her about causality but maybe she wasn't aware either. [right] Um, I find personally that correspondence from site to site [really helps] yes, it makes a big difference. Now in terms of the investigators, I don't know how much difference that would make for them. **(feels communication from site to cite is more beneficial to clinical trial nurses)** So here they would be the ones actually assessing the causality. But for me it's nice, it's nice to know, kind of a heads up as to you know this could happen, it's happened here it could happen there. That would be helpful I think, just having some sort of a streamlined process into, coordination and communication with other sites. That's really the only other study I've been involved in where I've had the opportunity to do that on a fairly, not really, a fairly regular basis. So it's nice, it's a nice option. [good]

M: What about in terms of gathering information from patients and kind of overcoming that challenge, what do you think would help there?

S11: Oh gosh, it's hard to say, again, every patient is different. Some patients, um, some patients I think it's easier to leave everything open and let, just leave it as a blank slate, let them tell you everything that's been happening. Um, some patients if you do that won't tell you anything. So some patients, not prompting but some patients you need to I think go through a list of questions and ask them about specific side effects, problems, even possibly body systems and leave it open that way for them to suggest things to you. Um, again, um, I find it's, again reporting is very different from person to person in terms of the clinicians. So I have to wonder would it be detrimental or beneficial to go in together in terms of clinical trials nurse or clinical trials associate as well as physician? Go in and do a small portion of the assessment together [mmm hmm] even if it's an AE or toxicity assessment before the physician does their full physical, things like that. Um, just so there's a general consensus and everybody can talk about it together to really understand what, what the patient is experiencing. Um, and again I think that's very subjective for the clinician also the way the patient describes things. I could consider it a grade 2 whereas the physician could consider it grade 3. I realize here that the physician overrides our opinion obviously, which makes totally, total sense. [mmm hmm] Um, but again, if it's very different [yeah] grade 1 to grade 3 it's hard to, to determine where it's really falling [yeah] one extreme or the other or right in the middle like a grade 2. Um, so I wonder if maybe collaborating a little bit more in terms of doing the AE assessment together if that might make a difference. [okay]

M: Is there anything else that you think might be helpful in terms of making that whole causality assessment process a little bit easier or streamlined?

S11: Um, yeah, depending on how much you know about the drugs specifically and whether that be through the IB or safety reports or what have you. Um, I

think giving the patient a little bit of background knowledge first and giving them an idea as to, you know, instead of just leaving it very broad category, well you might experience some nausea, but maybe making it a little more specific in that, not too specific because obviously they have a lot of their plate. But more specific in you know, essentially what, what we would consider being very serious. Not that we don't do that already, but maybe just making the lines between, that might be hard to do, between gradings. [mmm hmm] You know, there is a really big difference between feeling a little bit nauseous in the morning and feeling nauseous to the point that you're vomiting 14 times a day. But actually explaining to them those differences and why we consider them so different. And how important it is to tell us all those little things, things that you know precluded it or made you feel better, that sort of thing. **The professional asking the patients questions can really impact the decisions being made by the information they solicit**) But being, I think maybe just a little bit more specific with the explanation of things to patients. Again, I'm not really sure that's optimal especially considering how, you know, little time everybody has these days. And again, a lot of these patients, it's, it's fairly new in that, they've either just been told their palliative or that they even have this disease or that sort of thing. Like maybe it's not appropriate at that time. So I think that, that would be a little tough, but maybe giving the patient a little bit more information to work with [right] might make it a little bit easier to understanding how important it really is for us that they tell us everything. [mmm hmm] I think that, that's um, and I think a lot of patients don't want to disappoint which I think is really too bad. And you can say it over and over that we need to know for your own safety, but I find that a lot of patient's they [who don't they want to disappoint?]. I think their physicians they don't want to disappoint, um even probably clinical trials they don't want to disappoint. I also think too um, in Phase I situations where, not always, but a lot of the patients are end stage palliative, they've, a lot of them have come to a point where there aren't any other treatment options. I think it's a distinct possibility that they could very well minimize things because what they're thinking is I'm not going to have another treatment option if this fails me. Which is part of

what I experienced with, with one of my IND patients, um, [tell me about that]. He was actually the gentleman with the rash. He found out, not even a year ago that he had essentially stage IV liver cancer, young guy, early 50's, was finding it really hard, even though he had a history of cancer in his family, was finding it very hard to come to terms with the fact that he was sick. Very much a go, go, go type person, worked every day, all day, never slept by choice, just because he liked to keep busy and do as much as he could with his life. Um, so once the IND study failed him, um, I mean he told me every reason in the book why, even though according to our, our measurement criteria, he understood that he had progressed according to the study. But he felt great, you know, I don't feel unwell, I don't have pain, I'm not sick from the chemo, I have, you know, could we not just do one more, could we not do more? Um, so I think in terms in patients coming to terms of what that means to them, especially, again, especially in early studies where you want the least sick of the sickest people. It's a tough population to round up in a place like this because we are a relatively small centre in the realm of things. **(Patient education would aid in attributing causality)** Um, you know, have a huge population like that but like I said, I think, you know, having younger patients who essentially are told they don't have any other treatment options, I think that's tough for them especially when you're going to be taken off treatment because of toxicity. I think that's hard [yeah] I mean I think it's hard for everyone involved, but for a patient to admit you know, even something as simple as nausea or something we might take for granted like vomiting. Um, that can easily take you off study but for a patient who knows there is nothing else out there I think that can be pretty devastating. [yeah] So I could [so that would maybe lead to them minimizing] I think possibly [the adverse events that they're experiencing?] I wouldn't be surprised if it didn't. [okay]

M: I just want to talk a little bit about, what do you think the implications are to assigning causality poorly?

S11: Oh, I think there are huge implications, huge. Um, I mean to start out with the very basics, a lot of, a huge workload involved, um, in doing it poorly and that, I mean it could be anything. Just from the workload involved in SAE's, even the reporting, all the different avenues it needs to go through. Um, an implication could be the fact that drugs aren't being marketed or aren't moving on to different phases of trial because causality has been improperly assigned. It could also on the very opposite side of the spectrum, it could also lead to harmed patients, it could lead to death in patients. A whole array of things, I mean it could obviously affect the statistical analysis of the study, it can affect everything. I think that's huge to be quite honest with you, I think that there would be **(misattributions have serious implications)**

M: What are your concerns about how clinician are currently assigning causality, do you have any concerns?

S11: Um, not specifically, nothing specific but I think it would be very possible and again I don't know again exactly how other centers work. Um,

M: Just in your experience have you had any concerns about how it's been done?

S11: I think it could be possible that maybe things could get not necessarily overlooked but a very quick look, take a quick glance at you know, maybe what somebody else has written. [mmm hmm] Um, and you know it's very easy to just sign your signature and walk away. **(feels those you sign off on attribution don't give the study the attention it deserves)** Um, I think that, that could be a problem, um, I also think it could very well be problematic if things get lumped together. Oh, patient A experienced this and I thought it must be related so if patient B is experiencing it, it must be related too. And again, I don't know how often physicians do that but I think it would be a possibility. [mmm hmm] Who's kidding who, they're busy and overworked, um, and trials are a lot of paper work.

So I think that's possible, I certainly don't think there would be malicious intent [no] but I, but I do think that you know, even time constraints that sort of thing could have, play a factor in that.

M: What do you think we could do to make it sort of less time consuming or how could we ensure that it's not done too quickly?

S11: Um, I don't know, I think that again is an individual physician thing. I think each physician has different interests in different areas and studies for different reasons. [yeah] Um, I think some are just more motivated than others, um again, every person is just so very different, that's the problem with medicine is everything is so individual. So I'm not really sure, in terms of, again schemas and that sort of thing for known causality or what's expected in terms of a trial that would be great. Even in terms of the IB and having, just something that was a bit more comprehensive. You don't necessarily have to read through an entire paragraph to figure out that nausea is related to cisplatin. I mean if you had tables that were easy to read instead of actually having to read everything which is great when you want to read it it's there. But if you just want a quick reference that that's available for you also. I know in terms of my work and again it's not causality, it's other things, but I know that it's a big timesaver. But to have it maybe printed right, right in the IB I think is just a bit more surety [mmm hmm] you know. You know that it's right there and it's visible and accessible. [yeah, okay]

M: Let me see, now I guess, I know you don't attribute causality yourself [yeah] but I'm sure you're familiar with the various causality scales and the way it's attributed right? [yeah] So can I just ask you then to consider a scenario for me? [okay] Okay, let's just say you're treating a 65-year old patient with a confirmed diagnosis of metastatic breast cancer [okay] in a Phase I clinical trial and she experiences a pulmonary embolism. [okay] How would you assign causality to the study drug, and I recognize that you [laughter] don't have a lot of information

[right] to go with, but let's say there was a 75% chance that the pulmonary embolism was due to the study drug [okay] and a 25% chance that it was due to other factors like [okay] concomitant meds, concomitant illness, disease progression. [okay] And your scale is certain, probable, possible or unlikely.

S11: Okay, so how would I, like my thought process in going through that or just what would I, right now what would I grade it? Like what would I give it in terms of causality?

M: Tell me a little bit about your thought process, yeah.

S11: Um, I mean essentially you just go back, the basic things, patient history, essentially the things you just mentioned, concomitant meds as well as intercurrent illness. Um, other things too, do they have a pic line, do they have a central line, have they had a bout of coagulopathy before. Um, so essentially all the very basic things that you know, any of us clinicians do in assessing a patient. Ah, um, even just going and asking a patient history, what have they noticed, is there anything different/, um, when did certain things start? Was it you know, did you have shortness of breathe before the infusion, after the infusion? and that sort of thing. Um, I think in this situation, I mean, 75% against the 25% and not knowing a whole lot about the patient's history obviously, um, I think it would be very easy to jump in and say probable or certain. I think it's actually more appropriate at this point to say, possible. Um, [so that would be] I would probably say possible [yeah] of course you would have to take in all the other factors into account but it's, it's a distinct possibility. Even regardless of what her past history is or not it's a possibility.

M: And what if the percentages were changed to a 50% chance that it was due to the embolism and a 50% chance it was due to all those other factors [right] would you change your assessment then?

S11: Um, at this point probably not, just with the information I have I would have to say no, again, possible, possibly not but again it's possible.

M: Okay, and what if it was a 20% chance it was due to pulmonary embolism and 80% chance is was due to other factors. And I know that it's a very hypothetical situation [yeah] very difficult to say, but.

S11: Um, 20% chance, I would probably stick with the same but again investigate a bit. If other things came about clinically that, I mean you could definitely pinpoint it to not likely, then that's probably the way I would go. I mean if she had some sort of a history of coagulopathy I would definitely, I would go more to the not related end. But if there was absolutely nothing and it was just very middle of the road 50 or 20/80 and still nothing else, I would still say possible.

M: We're just trying to get a sense of um, [yeah] how people assign to those categories [sure] and you know try to quantify [yeah] what they mean.

M: What I'd like to do now is just ask you a little bit about your experience as a clinical trials researcher. [okay] In which cancers do you specialize?

S11: I am hematology [yeah] currently I am doing the hematological studies, I do the melanoma studies. I do, I was doing the liver studies and prostate.

M: And you have a Bachelor's in Nursing.

S11: I do.

M: And what year did you get that?

S11: Graduated in 2003.

M: And you have your RN license?

S11: I have my RN license as of [what year did you get that] 2003 [the same] as well as my um, certification in oncology nursing in Canada [is that CANO] CONC is what the, my designation is.

M: And what year did you get that?

S11: Just, 2006 [good for you] thank you.

M: And so what year did you become involved as a clinical trials researcher?

S11: 2005

M: And what percentage of your work time would you say is devoted to clinical trials, 100%?

S11: In terms of, what else would I be doing? [laughter]

M: Well I guess you're pretty much a dedicated clinical trials nurse.

S11: 100% dedicated yeah.

M: And of that, what percentage of your time is devoted to Phase I and II trials and what percentage to Phase III?

S11: I would say right now and this could very well shift quickly once we start to accrue onto the Phase I. But Phase I/II I would say right now is [just roughly] I would say right now approximately between 25 and 30%.

M: And the other 75% would be Phase III? [yes]

S11: Like I said though I think will actually be the opposite come about a month from now. [so things could change] Yes, very much so.

M: And can you tell me about any training you've received specifically with respect to assigning causality to adverse events.

S11: I've had no formal training [no] actually.

M: So how have you learned about it?

S11: I think just my past experiences, personally and again I don't know any different. But being a nurse and working on the floor and giving a lot of cancer drugs, um, the huge variation of cancer drugs to a huge variation of individuals, all adults, mind you I was never in peds. Um, but ranging in age from 18 to 100. You know, just my past experience, what I've seen, I've learned you don't jump to things too quickly but assessment is the most important part of your clinical work. Um, and whether that be assessing causality of something or just assessing symptoms. [mmm hmm] I am a very firm believer that, that is the most important part of your day. And, and researching into that and taking nothing for granted and you don't take somebody else's word for things. And you certainly don't take credit for something you didn't do. So I'm very much into, you know I have to look that up, it's not, you know, you never stop learning and it's not something you can take for granted. Even if it's something you've seen, you know, 100 times over it's still worth investigating each and every time [yeah] so. **(certainty is difficult to achieve, even for those with experience)**

M: What additional education do you feel would be helpful to clinicians like yourself?

S11: Um, having some sort of formal training in that. Um, we get lots and lots and lots of formal training in good practice guidelines and I personally have had lots of other training in doing ECG's and even how to fill out CRF's. I mean almost every other aspect of the trials that I think we do here we get lots of training in. In terms of that I think because we're not responsible for that, I think it kind of gets a little bit overlooked. [okay] Which personally I do not think is, the most optional approach. I think it would be extremely beneficial to have, for the CRA's (**Clinical Research Associates**) here at our centre, I think would be extremely beneficial to have more formal training in causality. Even for myself, even though I think I have a bit of more broad knowledge base in specific chemotherapy drugs or classes of drugs. I think that that would be very important, even

M: What would that look like then?

S11: The actual training you mean?

M: Yeah, what would you think should be the content of it?

S11: I think, gosh that's asking so much, almost, almost quite honestly almost like a pharmacology course, um. Essentially to teach you know, different types of drugs, different classes of drugs. But also in what types of cancers, disease sites, you know histological types, you know what are we treating with what and why? Um, even how they've proven to be effective, um, I think really understanding what they effect, how they effect, if it's the cell cycle, you know protein synthesis. Whatever it is, I think it's very important to have, I mean at least bare minimum a small amount of knowledge in that to be able to make fair assessment in that sort of a situation.

M: Yeah, so like the biological mechanism.

S11: Yeah, well definitely because each mechanism affects the person's body differently. And again, I don't think that, I don't think that as a group we know enough about that, I think we're very lacking in that area. [yeah]

M: And what sort of, what do you think would work best in terms of a forum?

S11: It's hard to say. I personally am a more visual learner myself. You know, I take quite well to lectures, I like that sort of thing. Lectures, handouts, even you know, online courses, I think that would be very valuable. Actually just coming back to what do I think would be valuable, assessment skills I think would be very valuable in improving skills in causality. And you know not necessarily to determine causality itself but just to get a full assessment of whether it be each body system or each AE. I think that there's, again, I think there's a lot of room for error in assessment skills and I think that, I mean everybody is going to be different but I do thing that you know, teaching the proper avenues or even types of questioning I think could maybe improve things quite a bit for our department specifically.

M: Yeah, no that's, I think you've touched on something important there, definitely. Okay, um, I think those are all the questions that I have for you. Do you have any questions for me?

S11: I don't think so [no] no, I think it's definitely worthwhile. Again, I think our department is very different from all the other places you're going to visit and all the other people you're going to talk to. [yeah] So it's, I think it's probably tough to modify what you have to fit us too. [yeah] But it's, it should be interesting hopefully for you in that we are so very different from everybody else [yeah] and the way that we do things here.

M: Well, I don't really see that as a barrier [great] I mean I think there's probably going to be a lot of similar needs despite the differences. I think there's probably

going to be quite a [good] you know it could work in any model. [great] Okay, well great, thank you.

Subject 12

M: So I'll just start with a little bit about what it is that we're doing. We're interested in how investigators assign causality to adverse events specifically that occur in the Phase I oncology clinical trial setting. And the idea is that by gathering a little bit more information about that whole reasoning and thought process and the issues surrounding it we can potentially develop a tool that might help to sort of systematize that process a little bit better. And so um, yeah so we, and the goal with the tool is that it would sort of help clinicians efficiently and reliably assign causality. [good] We feel that by better understanding the needs of clinicians we can make this tool more relevant to clinicians. And I understand that you're not maybe practicing as a clinician [yeah] at this stage, is that correct? [yeah] You are still?

S12: Oh yeah, I still have, not like before but ah, a half-day clinic a week but that's only, very busy before then.

M: Right, okay, so you've got lots of experience then and would have lots of good insights in this. So that's sort of what we're trying to do and um, so I guess I'll just start then [yeah] is that alright? [sure]. So let's say for example you're an investigator on a Phase 1 oncology clinical trial and a patient has just reported experiencing an adverse event to you. Can you just walk me through how that situation is handled and the reasoning you go through when you're assigning causality?

S12: The ah, I guess there are several components that have to be considered, I guess first is getting a clear description of what the event is, the nature of the toxicity and what the severity of it is. What the series of biological consequences are, in other words a problem that can result in a respiratory component, a kidney

problem occurring etc. So the systems of the body are linked. So basically you want to define the scope and the severity of the problem. You then, I think want to understand result from diseases. The nature of the disease in terms of the problem that is occurring. Is there a potential linkage where the problem relates to the disease? Secondly, sort of linked to that what's the status of the disease? [right]. Is the problem that you're being faced with in fact a toxicity, but in fact it's a manifestation of the disease. Am I talking too much? [no, you're doing really well, I just wanted to make sure it was still working] Is it a manifestation of progressive disease as opposed to not due to, or the intervention? The sort of next level is somewhat related to that and there are sites, groups that would have problems with that, but within hematology part of the disease process you often face consequences with an infection [right]. Infection is a common part of the disease process. So you've got primary problems of the disease, problems of progressive disease and then sort of downstream consequences that occur as a result. **(Many confounding variables to consider)** Next step I think would be to look at the nature of the treatment received and have they received single modality, multi-modality, if it's a single modality it could be a single agent or multi agent. In the context, in the Phase I study, often Phase I studies are single agent, but you do Phase 1 studies with combinations. So then you have the whole issue of what's the investigational drug versus what are the known consequences of, of the other components of the treatment. You have to understand the potential, the potential toxicities of, of those drugs and what would be expected versus would be unexpected. Under expected you probably still have varying degrees of severity, so one problem may be [4:10 skipped] with a given level of severity you may be seeing in your individual patient disproportionate to what's expected. So through the sort of disease status, the disease indirectly, the nature of the treatment, what's expected from the treatment, standard parts of the treatment. What would be expected as part of the investigational agent. So if it's anticipated that or if the investigational agent is well known to cause neutropenia or whatever and you're seeing neutropenia it wouldn't be hard to imagine a cause-effect. One of the final steps then is um, looking at timelines and surrounding circumstances.

So you've got a problem, a clinical problem does it fit a logical timeline with respect to exposure to the drug or possible timeline of exposure to the drug? **(again, timing plays a major role in attributing causality)** Secondly, have any other things in terms of co-interventions been done in terms of management of problems that have come up along the way. For instance, if a person gets a skin rash, they got a drug, they, they may or may not have had an infection, they got put on an antibiotic and they got a skin rash. So you're, you're situation is now confounded by that. It's important that you look at it in terms of temporal relationships but other relationships with co-interventions. So I may have left some stuff out but those are probably the major parts. **(there are other smaller factors that play a role when assigning causality)**

M: When you're going through all of that thought process do you use any tools to help you or is it just something that you kind of go through mentally in your mind?

S12: The tool, well um, okay, if, if we back up in terms of the effects of the disease, there's probably not tools about, you know, you're supposed to know the disease you are looking after and if you look after lymphoma or myeloma there's content knowledge there. **(feels responsible for knowing the disease without the support of a tool)** I suppose there, there could be rare instances ah, cerebellar degeneration is an extraordinary consequence of having ??, so you know, if you weren't to know that and they got a therapy and is it blame the therapy? Some of the tools you might use would be a lit search type of in terms of the feature and, and of the event itself as a downstream effect of the disease the argument would probably still be the [6:41] the um, consequences of the drugs, standard drugs or investigational drugs, um, you would have, if you were in doubt, I guess the first tool would be the protocol, the study protocol would have aspects of that. **(tools are a source of support when in doubt)** If it's new and uncertain, the study protocol, nurse assistant, clinical trials nurse, knowledge of the study protocol, coordinating centers' knowledge of previous experiences, lit search.

M: When you say the coordinating centre do you mean like the sponsor?

S12: Yeah [yeah] sponsor's aspect.

M: Would you sort of, would you call them up?

S12: Not necessarily first off, I'd probably go to the protocol, the investigator brochure, ah, their collaborator, ah, their collaborators that have, if we're the centre, then myself and the study coordinator. If I'm not the PI, I would speak with the PI at that centre to deal with that but in terms of other tools they'd be the protocol itself, the investigator brochure, lit search material, the sponsor, CTEP, the provider in terms of the nature of the toxicities in terms of severity, you know the standard grading and those are probably ... **(identified many resources but no distinct/standardized tool)**

M: And what about for actually assigning causality? Do you ever, I know there's like the criteria for grading severity as you mentioned, um do you have any sort of a tool like that for assigning causality, are you aware of anything?

S12: Not in terms of grading, in terms of definite. [yeah] I mean schemas for that and assistance for, other tools that [8:23] in finding those, in terms of the focus of the study to be honest with you.

M: Can you give me an example of a schema, you said there are schemas for the probable, possible or just the actual scale itself [that's right] that's in the protocol.

S12: In the criteria, yeah [laughter] there's variation in filling in, of the criteria people would use. And I'm sure there's [8:46]

M: That can lead to, you know is that a concern for you?

S12: Um, yeah, obviously in terms of the integrity of the study, the generation of serious adverse events and bringing the implication of who should report them, the consequences of reporting it in terms of the potential outcomes influencing study design to capture it [what implications] in case there's something of high risk. **(feels reporting comes with consequences)**

M: You mentioned the potential fall out in the study design, can you just elaborate on that?

S12: So if, if, there's an SAE that, that comes out of that, that has implications for notifying sponsors, the sponsor notifying the regulatory agencies and the company, there's timelines for doing so. The nature of enough AEs may influence the conduct of the study [how does it influence?] so misrepresent, well a series of SAEs may [9:51]

M: Have you every experienced something like that, can you give me an example or tell me about it?

S12: Um, we've, we've ended up closing the study to accrual because we had frequent dose-limiting toxicities which in themselves are not events, they were potential consequences brought to a more profound degree and the dosage required adjustment. But along the way with that, we had an SAE, one of the consequences a patient became, the first person to start with it got a bad disease etc, etc, a subsequent death occurred and study treatment was attributed to that. Had the DLTs not already closed the trial to accrual to start and having to re-design, the SAE would have. That was sort of the freshest in terms of [10:40]. Now if you were to turn that situation around, if he had been very ill, and met the eligibility criteria but is a high risk person and you attributed the subsequent poor outcome to their disease and unrelated to the treatment, that would be a stretch. I mean things are truly unrelated that would just you know, blow over. So you

could in one situation attribute something to an entire one set of the, the most serious and if it's this and you don't acknowledge it, that's dangerous for future patients in the study. [right] If it's, if it's you know, this and you label it as this, you could be potentially closing a trial that presumably was well thought out and had a good hypothesis and the hypothesis could end up being rejected. [implications] Potentially [yeah] I mean if you polarize the extremities yeah, most of the stuff is not going to end up being that extreme, it's going to be in the middle but.

M: Have you any concerns about how causality is current assigned?

S12: Um, yeah, I think sort of along the lines of what we've just talked about [yeah] that um,

M: How about the way in which clinicians assign causality, feelings of

S12: Yeah, I don't think the, the I don't think amongst clinician investigators that, that a sufficient set of details to consider would be uniformly[12:20] constructive.

M: When you say category what do you mean?

S12: Unrelated versus definite or possible, what's the difference between possible and probable? [right]

M: So those terms aren't very clearly defined. [no] What do you think would help in assigning causality, that might be one thing I guess, to better define those categories.

S12: I think what probably needs to be, I mean you can make errors in either way right, assigning it when it's not present and not assigning one when it is present. So there probably needs to be a philosophical agreement as to which type of error it is conceivable that, that could the error change in different situations. In

prevention trial the bar for causing no harm is set very, very high. In hormone replacement therapy in women you know, the bar would be set very high, because harm, that's going back, it's going to play out to a lot of people. If you have somebody with acute leukemia where you know, say relapsed acute leukemia, where the life expectancy is 12 weeks and the benefits of treatment are debatable. Do you have a complex disease and a complex set of circumstances for comorbidities based on a, you know, the type of error would vary in the situation. So I think there's a, overall there's a set of principles as to [13:54] **(I wish this didn't skip)** about making that maybe and so there has to be. Once you understand which is the sort of area within given.

M: I see where you're coming from, just depending on philosophical standpoint and your willingness to accept harm or [yeah] yeah [yeah].

S12: I mean that's life, that's risk and benefit and acceptance of taking greater risks. **(feels they need to accept risks in order to get the job done)**

M: What external influences from third parties have you felt when assigning causality?

S13: Um, the most, um, the first and most immediate is the work the clinical trials nurse is going to have to do. [okay] It's just very practical and if ah, I mean there is a bureaucratic process that is time consuming that if you assign an SAE versus not that somebody's going to have to do a lot of work and meet timelines and set a whole ball rolling. So that's, it's not an external pressure but there's a reality [right] that, that you have to factor in. You, I think you deal with that one pretty quickly and, and you do the right thing and if somebody has to do more work then so be it. But, that, that's the first most immediate one. I think you then have the issue of the sponsor, and sponsors, sponsor may influence. [okay, how so?] I think in general from what I've seen, sponsors will tend to, tend to things that are expected, the, if the consequence is an expected one and it's tended less to be

labeled serious adverse event even if it's expected but the degree and the severity wasn't, that's a tricky one, you give an agent [can you give an example of that?] Oh, to make an exaggeration, you give a drug and it's known to cause a low white count, neutropenia. An average duration of that's going to be five to seven days and it would be very unusual for it to last more than 10 to 12 days. If it's a new agent and you get neutropenia that lasts 25 days, that expected, is it expected or not expected. Well the neutropenia was expected, the severity was not. Now I suspect some people would argue with me, an extreme group would argue with me on was it serious etc. But I've polarized it with an exaggerated example. And you know at what point, well if it was 13 days, 15 days you know, sort of where's your cut point [sure] before you say it's expected versus unexpected. **(difficult to grade severity)** And I think it's in that degree of gradations that, that you can get debate and [differences] differences in interpretations.

M: So the sponsor would tend to oh that's expected.

S12: I think on the, yeah. Now I'm doing, I'm looking at it from a standpoint of clinical trials. For prevention trials, I don't know, I haven't done prevention trials. And what I said at the outset about philosophy, and which is the greater error, I'd have to see how that played out. [yeah, yeah]

M: Any other external influences or pressures that you felt?

S12: Not that I felt, I mean I can imagine things in terms of the hospital, the REB, if the sponsor is not a pharmaceutical, if you're studying a drug but the sponsor is, like the CTG and not the drug company. The drug company, they're all potential stakeholders within it. But I can't say I've sort of felt pressured, I think your original question was have you felt influenced by them, personally I haven't. But in, in, theory could you?, I suppose you could. The Regulatory

Agency itself [yeah] Health Canada, could you? yeah, yeah. **(suggesting others may have felt pressured)**

M: Have you ever heard of a tool developed by a researcher named Naranjo? There's a researcher named Naranjo who developed a tool to help clinicians assign causality to adverse events. And what I would like to do is have you take a look at it if you don't mind, and um, it's here somewhere, here it is. If you could just take a look at it and then just cross out any, any points there that you feel aren't relevant to the Phase I oncology clinical trial setting. There's no right or wrong answer [mmm hmm, no]

S12: They're all potentially relevant, um, I mean, any that are not relevant? [yeah] Um they're all potentially possibly [okay] um.

M: Are there any that you feel are more important than others. [yeah, yeah] Okay, so would you be able to just rank them along the side then, so 1 would be least important and then 10 would be most important and you could just sort of [can any of them have the same number or not?] sure, whatever you feel, 1 is least important and 10 is most, sure.

S12: I don't have to do them in order I can just give sort of a ballpark figure [yeah] as I muddle along. [great thanks]

M: So did the adverse event appear after the suspected drug was administered you ranked that as 10, that has to do with temporality.

S12: Yeah, if the adverse event occurred [it's pretty obvious] before that's a tough sell. I mean could you, could it have occurred and then been made worse by the offending agent. There's even interpretation about that one but. But it is occurred in it's full blown form before the drug was given the temporal profile [10:53]

M: Was there anything here, like did you think that there were any questions that were missing that maybe should be added. You mentioned the worsening which I don't think is in here.

S12: Well it's talks about test/re-test doesn't it and it talks about dose, which is, is there. [anything else that should be added?] Would probably [20:18 #5] in terms of the disease, so that the scope of what's considered alternate explanation. [yeah, that's a good point] That's ah, some of them, like the drug concentration in the blood, if you have that, that's potentially helpful information as a rule. Not having it, like even having blood tests with non-toxic levels would barely persuade me compared to other things [right]. So you have to sort of read some of these very carefully [sure] in terms of how they would [20:55] I'm not sure that ah

M: Okay, but you've never seen this Naranjo scale before? [no] Okay, this is the thinking that maybe we could adapt something like this to the oncology clinical trial setting and. What do you think about, do you think this would be used by clinicians? Do you think something like this would be helpful or do you think it's too cumbersome?

S12: I think it would, I think it could be useful and so it would be desirable to have something like this to, to um. **(finds the concept of a tool desirable)** Let me backtrack, I think it would have to be tested [yeah definitely] and is it, could you, is there enough reason to hypothesize it might be beneficial if adapted. Ah, I think that's a good hypothesis. The difficulty is each question you go through here, I mean, are you, are you just sort of downloading degrees of interpretation and variation around interpretation into additional components. So you know, it would have to be tested that it actually does lead to consistency. You know, you would almost have to have a two-sided statistical test, could it lead to more inconsistency? it's not impossible. Because you could interpret, you know, you

could have degrees of interpretation here and it's kind of like um, you know, assessing quality of life you know, do you ask two questions to get an overview of quality of life. Or do you ask 40 questions that test domains, and what's the truth? [yeah] And what leads to more variation than the other. [right] And is someone's you know, is there a process where overall Gestalt could be made more consistent, or is this a bunch of components. I think you'd have to test it. [mmm hmm] But, but I'd be open to you know, I think it would be rational to think this would lead to more consistency and is worthy of testing. Now would, if the test and test circumstances showed that it was, that led to more consistency that would be great. Would people actually use it?, that's a separate question. It's um, just reading through it here in terms of test purposes, it's, you have to think [yeah] a lot about this. And to sort of go, now, it may be helpful to have the actual example in front of you right now that it's easier in the context of a given example and so forth that you go through it quickly. But for sort of [23.33]

M: Yeah, definitely. Okay thanks. And then the last little thing I'd like to ask is a little bit about your clinical, your experience [sure] as a clinical trials researcher. So you said you specialized in [hematology] hematology right. And you have your MD obviously right? [yeah] And what year did you get that?

S12: 78.

M: And when did you get your medical oncology license or sorry hematology license?

S12: It was 84.

M: And do you have any other Masters or PhD or clinical trials, no.

S12: I did some Masters courses but I didn't finish the program [at Mac?] yeah [yeah, okay]

M: The ClinEpi [yeah I did the coursework] A was the same actually, [yeah he was] that's okay you still got the education [that's right] And what year did you become involved as a clinical trials researcher?

S12: Where you're actually responsible, 84. I mean you would be exposed or exposed would have been as a resident even before then and 84 when you actually had to [24:40]

M: And when did you do the ClinEpi course work [um late 24:44] Okay. And I know this has sort of changed recently, but what percentage of your work time would you say is devoted to clinical trials?

S12: In terms of answering, for the purposes of answering this question you should probably use my old life [okay] because that's the experience, that's what's formed the basis of [yeah] not all but most, I mean I have learned stuff in the last [25:07] but if you look at that. Clinical trials [yeah, what percentage of your workload] depends how you, because I was a site chair in terms of for NCIC for hematology so I operate in, actual putting patients on trials versus developing trials, overall conduction of trials [everything] analysis. Everything [yeah] I was probably a day a week, 25, 20 to 25%.

M: And then of that, how much of that time was spent in Phase I, Phase II trials versus Phase III. [] Like out of that 25% [25] of the time yeah. [less than 5] Okay, then the rest of it was Phase III [Phase III].

And you've been a local PI obviously [yeah] before, yeah.

Then, I just want to ask a little bit about the education that you received, specifically to do with assigning causality. Can you tell about me anything you have received, any kind of training? How did you learn about it?

S12: Just by being around, it's informal, [okay] being exposed to certain **(learn through exposure)**

M: What additional education do you think needs to be made available to clinicians about assigning causality?

S12: Probably [26:29] other than that? To participate in USNCI studies you have to go through a web based, and certificate at the end, otherwise you can't be an investigator let alone a principal investigator. There's probably, there's similar training that's going to take place in terms of GCP clinical practice in terms of conduct of trials. [it's not in place yet] It's not in place yet [but it's coming] it's coming. There's probably modules within overall conduct of clinical trial aspects like that, as opposed to a specific education experience of learning about causality and assigning of events. It's probably a module in a broader sense of being an investigator and what the responsibilities of an investigator are.

M: So the Canadian investigators they do the, the USNCI training [for ethics] oh okay.

S12: We have, actually it was through this office, through LS downstairs has developed something that will be on the web

M: Okay, so the GCP is being developed here in Canada [yeah 27:37] yeah, that was, in previous interviews people had mentioned this type of education and thought that it would be really great to have something like this [yeah] as a module or on it's own to do with assigning causality.

S12: This is sort of a handbook on GCP and I'm just wondering what's [are those the ICH guidelines?] yes, I'm just wondering what's in here [skipped] but I will, I'll have to [they tend to define adverse events, serious adverse events] separately but I was interested to see because this is the type of module where

that type of training would be part of, now that's so regulatory driven I'm not sure that it's academic enough to incorporate things like this. On the other hand ultimately these are the things that go to regulators [that's right] so it would be reasonable [yeah]

M: Okay, great, I think those are all the questions that I have for you. [good] do you have any additional questions for me then?

S12: I don't think so [no, okay] that's a good idea. I remember A telling me about this, we sat beside each other and he was saying he was going to do this so it's neat to see that it's unfolding. Those were great questions.

M: Good, thank you.

Subject 13

M: So even the most experienced clinicians find assigning causality to adverse events challenging. Groups such as industry sponsors, clinical trial cooperative groups, they all expect prompt and sensible causality assessments. But as you know, it's not always that straightforward and if done poorly it can have large implications for patient safety and new drug development. So we're interested in developing a tool to help clinicians efficiently and reliably assign causality. We feel that by better understanding your needs as a clinician we can make our tool more relevant to clinicians. Do you have any questions? No, okay. First let's say one of your patients who is enrolled in a Phase 1 oncology clinical trial has just reported experiencing an adverse event. [okay] Can you just walk me through how that situation is handled?

S13: You mean mechanistically how it is handled? [sure] So for, do you mean an adverse event or serious adverse event? [lets say serious adverse event] So if a patient on a Phase I trial here gets, I become aware of a serious adverse event, then basically what I do is I contact the clinical [1:00] attempt to. Or, if for instance they come, they call us for something or they come in, and we obviously

see them here immediately and do the appropriate investigations. So we try to obtain all the documentation necessary to understand what the adverse event is, and fill out the SAE form and fax it to the appropriate um,

M: You said you gather all the pertinent information, so what sort of information are you looking for?

S13: Um, why, what event actually happened so the diagnosis, what diagnosis was made, so any supporting blood work, imaging, treatment the patient received and um, what consequences or what [1:36]

M: So you have to complete the adverse, the serious adverse event form [mmm hmm] and you have to assign causality. Can you just walk me through how you go about doing that, what you're thinking about causality?

S13: Um, well I guess, I mean, yeah, the bottom line is besides documenting the event, I have to admit that is very subjective at times [1:55] and how one goes about it or at least how I go about it is to understand what the known side effects of the agents are. **(helps to understand the agent under development)** What the possibility is in terms of if that drug could have caused that event. For instance if the patient is admitted for febrile neutropenia and the drug is known to cause neutropenia, and there are no other precipitating agents like the patient has not taken any treatment that they're not allowed to on the trial or any other unknown treatments, lets say naturopathic. Then it's almost an association by exclusion, so you exclude other things and then you basically make a judgment. **(it's really a process of elimination)** So again if a new Phase I chemotherapeutic agent is known to cause neutropenia and it happens in a timeframe that you would expect and there is no other agent or other agents the patient has been exposed to then I think you would have to say it's related. Part of the issues in terms of associations is there are various I guess gradations of association unrelated to related but then there's, possibly, probably or kind of,

you know, it depends on the grading or it depends on the association. That's very vague in-between. Two extremes are more, is easy perhaps to understand. Probable or unlikely always makes it very subjective.

M: Are there any sort of guidelines that you following when it's sort of that in-between?

S13: Um, well to be honest, not really I think you just go on what your best clinical judgment is or what your patient's status is. Um, what their co morbidities are and how their cancer is affecting them and what their pre-treatment symptoms are. You know if something clearly gets to the underlying, because really the problem is really sorting out is it related to their underlying disease or is it related to the treatment or something else which is less likely unless the patient is taking **(no tool to aid in uncertainty)** [right]

M: What resources do you refer to when you're assigning causality?

S13: None. [no] No, well I mean, I guess I shouldn't say that, none in terms of standardized criteria that's for sure. Resources, unless you mean basically going back to see maybe the investigator brochure and trying to understand some of the toxicities. I guess sometimes going, I think when it comes to a serious adverse event then more attention is definitely made to try to ?? that with whatever documentation you have. For adverse events, all the other adverse events grades 1-2, not only Phase Is but Phase IIs, there is no way that um, you get through every single one with the time constraints that we have. **(minor AEs are not reported due to time constraints)**

M: Is there any implications to that?

S13: Well there's definitely implications in serious adverse events, and, and association, obviously if you put it wrong then there's misinformation. If it is

associated and you don't think it is then that, that's probably the more harm there because we need to be aware, particularly in Phase Is that we need to be aware of and people think oh it's very unlikely I'm going to put it not related but then obviously that's information that the physicians and the patients in particular need to know about. **(feels professionals err on the side of caution and attribute causality to the drug)** So I think the worst is an association that is there but one grades as not associated and, and harm could be done to patients. The other extreme is people, and I see this a, a lot because you have to, as the PI on the trials you have to signoff on all the REB submissions to the REB. People that put everything is associated creates lots of paperwork. Where its very clear in reading through their SAE this was not drug related, this was disease related. And to me that doesn't do any harm to patients which is good but it creates extra paperwork for the CRAs, for the nurse, for us, for the REBs and to me that's more irritating when it comes from all around the world, you know you get. [yeah] People could be, could think a little I think, I don't know, think a little bit more clearer in terms of what they think is associated and perhaps those that are not associated would save the **(more attention and effort need to be put into causality attributions)** [right, okay]

M: And what about, you mentioned that you know with the lower grade AEs you just don't have the time to do the, to think about those ones do you think there are implications

S13: Um, obviously you want to have the most accurate information so implications aren't good data to come out. Um, I don't know, I mean I think we all try our best to see what we think is related or not. And I don't know, as clinicians we pay that much attention to grade 1 as we pay to grade 3 or 4. So I don't think the ramifications are as you know, anything [6:33]

M: Do you have you any concerns about the way causality is assigned, you sort of talked about over assigning causality?

S13: Over or under assigning, well I think the concerns, I mean I think concerns are definitely in this area that I think there is room if possible to be a little bit more standardized and rigid about associations and how we go about it I don't know. Maybe you guys can figure that out if that's what you're looking at. But ah, um, you know, I think it's a very subjective process, that's the problem. And subjective in terms of ranking them or associating but also subjective in how much effort people actually put into the work. And I won't say I do it all the time but you know, I think in terms of how much background work one does in trying to understand the causality with each one trying, if you're not certain, if you are certain it's very easy. Perhaps, if you're not certain are you going to spend that extra time to pull out the IB or talk to you're you know, pull out the protocol and actually do the best [7:30] **(feels some people don't but enough effort and time into properly assigning causality)**

M: What would you say are some of the problems or challenges when assigning causality?

S13: The challenges are particularly in Phase I trials these are, these, they all have their advanced disease, they often all have been through numerous other treatments, some of them have been heavily pretreated. Many of them are not of the greatest performance status and so they have a lot of other co morbidities or symptoms that can merge and play a role. Sometimes these brand new drugs we really don't know. We don't have a lot of information, that's why we do the Phase Is. And how much weight we put on what is seen or not seen in dogs or monkeys or whichever animal work they have done it on, large animal work done, kind of you know, there's not a lot of data there, so in the end if you don't have a lot of data to work with and you have patients, it does become very hard. [8:24] **(animals studies don't correlate perfectly with results on humans)**

M: Do you think more pre-clinical work needs to be done?

S13: I wouldn't necessarily say so because I think that um, um, I would like to see things being moved along in an expedited manner but I don't necessarily know that more work. I mean I think um, basically um, if we all had more time in our day it would probably be easier to do it. The SAE has to be filled in within 24 hours. I mean that's another issue, why 24 hours? what's the urgency? By the time we receive it, we send it off to the sponsor, it goes to REB, there's going to be a lag time anyways. And you don't expect things to, you know, maybe grade 5 toxicities where you have a death, maybe that should be 24 hours. But I, I don't know why an SAE can't be 48, so you don't feel that pressure to have to.

(doesn't understand why there is a 24 hour rule, not well explained) Not that, I think we do it just because we feel a pressure, but again I think we just said 24 hours and that's just been the rule that's been adopted all along right. [right] I actually don't see the rationale of 24 versus 48. If there was somehow, there was, maybe you know, particularly for Phase IIs because there would be a lot of data. But if there was somehow a unified international database where you could almost punch it in and see if things have occurred with that before then you would almost get a better sense that um, what the causality is **(no international database to aid in decision making)** Because if it's never been reported before for something, um, then who knows. I'll give you an example where we did a Phase I trial of an oral EGFR inhibitor, Tarceva, at a higher dose once or twice a week and a subject developed grade 3 effusions, pericardial and pleural effusions. I don't know if it was related or not, all I could really say was possibly because it could have been related. But again if there was a worldwide database for physicians who were the PI's on these trials to have their CRA punch in that. And if in the database there has never been a report of it then you probably have to say it's unrelated or unlikely. [mmm hmm] Versus if there were multiple reports of it, but they're all scattered, particularly at the higher doses and then you go well actually it could be related. So you know, that would be helpful because otherwise I'm going on an experience of N of 1 versus you know, if there's more literature.

M: Okay, anything else that you think might help?

S13: Um, I don't know, I don't know if they have um, I'm thinking rather than, rather than 5 different associations, I've got one here for NCI US, but again, you know, have um, [oh, the causality scale] yeah, unrelated, unlikely, possible, probable, definite. I mean I don't know if all of them are used the same or not. **(unsure if there are consistencies in grading measures)** But again, you have five relationships, do you really need to have five? Can you simplify it to three? So unrelated, definite, possible. Like what's the unlikely and probable versus possible versus probable, you know, where do you draw the line? Again, it's very subjective. So simplification would make it easier. **(too difficult)** I think simplification would make it easier in that regard. I think that um, particularly you know we get a lot for these Phase II/Phase III trials we get industry with drugs, particularly that have already been registered we get tons of these, for instance for capecitabine or herceptin from the sponsor we get lots of these coming to us and if they perhaps did a better job of screening them. If they saw something and they said this is definitely not related they would just go back to their PI at the site and say 'you know what correct this, this is not related so you don't need to generate an SAE' and you don't have to generate it from all around the world, do I really need to particularly if I don't think they're related. And you're basing, you're basing it on what a physician in a different country, who knows what experience they have in clinical trials or with the drug attributing a relationship? It's a huge amount of paperwork from it [the safety letters that you get]

M: Have you ever felt, or what external pressures or influences have you felt when assigning causality?

S13: Well I don't think I had any, well I think the only external pressures is obviously be accurate as possible. And so you know we're part of the, part of the Princess Margaret Consortium and you know a couple of the NCI trials, you know

the NCI physician from the US is emailing me in terms of causality, so obviously there are pressures to be as accurate as possible. But sometimes you really don't know if it's associated or not. **(pressure to accurately assign the inaccurate)**

M: So when they email you about your causality assessment are they asking you?

S13: Asking for clarification and they're making suggestions and they could, 'to us this doesn't seem related'. Which I think is not a bad thing, it's probably a good thing to be clearer on these. These tend to be, these tend to be more serious ones, dying after study treatment. I mean there are pressures to be as accurate as possible, try to get as much information, have autopsies and if they're dying in a different hospital you know, even though they are off study treatment but they're within the four weeks and so some information is not necessarily available. So there are some pressures, but I think, I don't feel they're undo pressures by any means, I think if anything that's a better way to go, obviously anything to be more.

M: Have you ever heard of an algorithm that has been developed by a fellow named Naranjo? I just want to ask you now if you wouldn't mind reading over these questions. This is the algorithm that was developed by Naranjo [you want me to cross them out or what?] Yeah just cross out any you feel are not related or not relevant to the Phase I oncology clinical trial.

S13: Not relevant, you mean not what I wouldn't want on there.

M: Well yeah, if you don't think it's, if you don't think it's sort of relevant to the Phase I setting. So now if you're done, with the remaining ones if you could try to think what you feel are the most important. Most important would be a 10 and least important would be a 1. Great, thanks. Can you just explain why you

crossed out 6 and 7, did the reaction reappear when a placebo was given. And number 7, was the drug detected

S13: I don't think most of the pks have a threshold dose as toxic.

M: And most important was whether the reaction improved when the drug was discontinued.

S13: If there's an antagonist you can reverse it now that's very rare but obviously

M: And least important was were there previous conclusive reports is that right? [] oh that's an 8, sorry [that's okay] was the adverse event confirmed by any objective evidence? What did you understand objective evidence [] I wasn't either when I read it. I think it needs to be made clearer for sure. [yeah]

S13: I guess, lab work or some imaging, something to confirm it with I guess.

M: Yeah, so this was one of the things we were thinking might help, you know because I think investigators tend to do this in their minds [yeah] but maybe not everyone so it might be good to have something to think about each of these things.

S13: The problem is if you are talking about an SAE you're not going to have a lot of that information in the first 24 hours and that's when you have to assign initial causality for an SAE. So usually, by the time, we're supposed to do it within 24 hours of knowing it so it could be later than that if it happens on a weekend and we don't know about it. **(could be more accurate in causality attributions if given more time)** Reality is that it's generally pretty soon after an event happens, a lot of the improvements or things like that we're not going to know about. I think you're right, most of us do use those criteria to assess causality in

a, perhaps not in a systematic way or a consistent way but we all that's how we all [think about it] attribute it.

M: And were there any questions that you thought weren't here that should have been? [16:20]

M: Lastly, I'd just like to ask you a little bit about your experience as a clinical trials researcher. So in which cancers do you specialize, breast?

S13: Breast, head and neck and Phase I.

M: And when did you receive your MD?

S13: I think I got mine in 1995.

M: And your oncology license?

S13: MD must be 93 and oncology is 99.

M: Do you have any other certifications [16:46]

M: What year did you become involved as a clinical trials researcher? [1999]

Overall, what percentage of your work time would you say is devoted to clinical trials?[16:55] [clinical work or all other associated work?] Anything to do with clinical trials?

S13: 25%

M: Of that, what percentage of that 25% [probably two thirds] and then the other third would be Phase III. Have you ever been a local PI? [yeah] And can you tell me about any training that you've received specifically with respect to assigning causality. [laughter]

S13:.....to be honest most of it's pretty common sense right, particularly with causality, definitely not. It's just here's the AE's, sometimes you go ask people if you don't really know. It's pretty common sense, it's just information that's all it is.
(just sees determinants of causality as information, nothing deeper)
(distanced from the meaning of the trial)

M: Do you feel that there's, it would be beneficial to have any education?

S13: I think um, you know in general, it's probably not a bad idea, most things we have to do are based things or CD based you know just a few things in there [17:48] just as important. Making people aware of how significant it is. People, I think, they just tick off one or the other just because it's the first thing [] without thinking about all the ramifications particularly all the safety reports that comes out of something like that. Yeah, I think it's not a bad idea, it should be done.

M: Those are all the questions that I have for you. [okay] Do you have any other questions for me? I really want to thank you for taking the time, I know you are very busy, that was great, thanks very much.

Subject 14

M: So even the most experienced clinicians find assigning causality to adverse events challenging. Groups such as industry sponsors clinical trial cooperative groups, research ethics boards all expect prompt and sensible causality assessments. But as you know, it's not always that straightforward and if assigning causality is done poorly it can have implications. So we're interested in developing a tool to help clinicians efficiently and reliably to adverse events that occur in Phase I oncology clinical trial. We feel that by better understanding your needs as a clinician we can make the tool more relevant to you. So do you have any questions [no] before we begin? [no] Okay, great, so let's say one of your Phase I clinical trial patients reported experiencing a serious adverse event. Can you walk me through how that situation is handled?

S14: How that situation is handled? [yeah] So the patient has reported with a serious adverse event. [yeah] What do you mean by handled, the formal process? [yeah, what are the next steps that you take?] Oh, well we usually take a precise and detailed history of the, of the event and then we usually dictate a report. And then it goes through the SAE reporting system that is determined by the study protocol and we have to assign a causality.

M: Okay, and what sort of thought process do you go through when you're assigning causality?

S14: What the process, my personal process is? [yeah] Well, um, it very much depends on, on the situation of the patient and the drug. If this is a side effect or a serious adverse event which clearly has been recognized as a possible side effect of this drug and the patient has no reason to have a symptom like that then causality is usually easy to assign because then it's very likely the event was driven by the drug. It's more complicated if the patient is in a situation where he can develop certain side effects by, caused by his disease and his personal situation. For example, if somebody develops a thrombosis and has extensive metastatic cancer and the thrombosis occurs at the same time on a drug which is known to cause that, then it's usually a question. But, but at the end of the day it's always about drug. If I'm uncertain whether it's related or not I tend to, for safety reasons, to decide to call it a drug related possible SAE rather than not.

(attributes to drug when uncertainty- method of coping with uncertainty)

[okay] If, if it is an SAE which is clearly independent because the drug is known not to cause those side effects or because it's obvious from the patient's situation that it's related to the patient's situation and disease then we assign unlikely. That's probably the exception in a Phase I situation. [good]

M: So as a general rule you tend to attribute the causality, if you're unsure.

S14: Um, well at least you have to assign a possible [yeah] I mean because you cannot really, you have to be honest and you cannot really rule it out. Even so that you often get the question back, are you sure that this is possible. Well yeah, it's possibly related or possible that there is a relationship because you cannot prove the opposite. [right, okay good]

M: What are the resources that you refer to when you're assigning causality?

S14: Um, history and depending on what the SAE is, additional tests, imaging studies, lab tests, which we, we utilize to try determine whether or not it's drug related. **(did not identify tool)**

M: Any tools to help you when you're assigning causality? [tools?] Like any decision trees, flow charts or algorithms. [no] Do you think something like that would be useful or?

S14: Yeah, [yeah] yeah I think so. [okay why?] Well because there's a, it may help you sometimes in the dilemma where you in this grey zone of serious adverse event where you think about what to, what to assign to this SAE. If you have a clearly unrelated or clearly related SAE that's easy but the, the vast majority of SAE's is probably somewhere in between. And then as I explained before, you have to, to somehow try to get as much information as possible and then put everything into perspective and then assign a causality. But that is basically based on, on the situation and your experience and not on any formal rules or algorithms or whatever. **(clinical judgment)**

M: In order for a tool like this to be useful for you what, what would it have to, what criteria would it have to meet?

S14: I think it should have all the, the legal implications in it, like, like GCP guidelines or whatever, certain definitions of certain, like the definitions for what

is a possible, possibly related serious adverse event, what is a related event and these things. And then, then probably cover the main categories [the main?] of those, of those events. Well I'm wondering whether you can develop a tool which helps you with certain situations. [can you give me an example of a situation?] Well if you have a patient with whatever, abdominal lymph nodes and the patient develops a thrombosis and is on a drug which, which has, is thrombogenic. Well is it because you have the lymph nodes compressing the vein or is it because of the drug? [right] That's one of those typical situations where I think, hmm, can be disease related, can be drug related. So you cannot rule out that the drug contributed to this so you have to assign a possibly or possible, relationship possible. And this, this is this grey zone where I think a lot of where those serious adverse events fall into and where you really don't have a good tool to help you. It's, as I said more experience and judgment of the situation. And I'm not sure we can develop a tool because what would a tool do in a situation like this? [yeah] It's difficult. [yeah it is a challenge definitely, okay]

M: What do you feel are the major challenges associated with assigning causality?

S14: Exactly that, exactly the situation where you, where you have different reasons on the drug side and the patients side for this particular adverse event. And you have to judge what is indeed the main cause for the adverse event. [yeah]

M: How do you sort of do that now?

S14: Well as I said, you try to get as detailed picture as possible so that you can really take into account every little piece of information. And then you have to weigh the two sides against each other. And if you, if you cannot assign a clear unrelated, then you have to go with the possibly related right away. I think in a Phase I trial you only should assign an unrelated or an unlikely only if you are

really, if you really have a good enough reason to believe that it is unlikely.
(seems fearful of stating that AE is unrelated)

M: What do you think are the implications of assigning causality poorly?

S14: Well you can clearly overlook, worst possible thing would be that you actually don't report a side effect which is actually a side effect, from, from the drug. That may really happen, but I think one of the existing problems is that the frequency of those side effects maybe under reported.

M: What's worse, overlooking it all together or

S14: Overlooking it altogether is certainly worse [yeah] but I think [it's also important] a serious adverse event, if a serious adverse event is seen in relationship to this more often then at some point we, we report it. But I think the frequency may then be under reported. But the key, overlooking a side effect or not reporting a serious adverse event which is actually part of the side effect profile, that's probably the worst, the worst thing.

M: Any other implications do you think?

S14: The opposite is true too, if you , if you report an SAE which is not related to the drug [mmm hmm] then that can cause a considerable, can have considerable sincere consequences for the, for the drug and the development of the drug.
(there are always consequences to misattributing)

M: What kind of consequences?

S14: Worse case scenario that you delay or you stop the development of the drug. I mean imagine that a patient dies on a Phase I study and you assign the death as possibly related to the study drug and it wasn't. Something like this can

kill, kill a drug in the development or at least considerably delay it or cause a lot more costs for the, for the company or whoever develops the drug to do additional testing and stuff like this.

M: Do you have any experience with something like that, can you tell me about a time when something like that happened or are you aware of anything like that happening?

S14: I have not had a case that ah, a serious adverse event was reported, wrongly, wrongly. No, I cannot.

M: Or just a time when a drug was sort of halted in it's development because of um,

S14: I've seen death on Phase I's [yeah] um, and, and that usually causes a lot of emails, a lot of regulatory things. And I've seen studies where the, the drug went back to pre-clinical studies even. The clinical development was put on hold for a year or two to get the drug back on, in the lab and do further testings there.

M: What are your concerns about how clinicians currently assign causality?

S14: Well it's so subjective, in the end, for the majority of SAEs which are in this grey zone of possibly or likely or unlikely related, it's a very subjective, a very subjective thing which is based on experience and, and of, of the investigator. [mmm hmm] **(sees subjectivity as a concern)**

M: Why is that a concern?

S14: Well because things can be wrongly assigned [yeah] with all the consequences. If you assign a possible, that's different from being unlikely so

that can have implications on the further course of the study and the side effect profile.

M: Any other concerns about how causality

S14: I was just thinking but ??????

M: What external influences or pressures from third parties have you felt when assigning causality?

S14: Laughter, boy you feel a lot but, you sometimes get, you sometimes get, sometimes, a lot of companies these days are actually very sensitive, I find, with these things and they, they are very open to discuss these things. Sometimes you get more than usual amount of emails with, do you really think this is related or not? But I never felt pressured, probably because I don't let it put pressure on me. [mmm hmm] I just tell them, that's how it is and that's how I think it is and that's how I think it is. [right] But I can imagine that, that happens. I also think things have changed a little bit. [yeah, how come?] Well I think a lot of companies are more sensitive for these things because the process is more open than 10 years ago. [yeah, how is it more open?] It's more open and more controlled, I don't know what, I'm from Germany and so I don't know about Canada. But in Germany the whole process is now much more monitored, much more detailed and has much more regulations on it.

M: You think that they're sensitive just because they're being watched?

S14: No, I also think because if, if they assess something like this wrongly [yeah] and it happens in the future they can have a big problem [yeah] by not having reported that and really, clearly outlined the process how they handled this. And especially in the US that can be very expensive, a very expensive thing. One of the examples is this Celebrex, Vioxx thing, where apparently some side effects

were kind of very generously [swept under the carpet] well, or at least not put open, put openly on the table and discussed. And ah, and ah, I mean that was a huge disaster. [yeah] And if they had done that before the drug would probably still be on the market and the benefit/cost ratio is probably still in favour of the drug but just by not doing this, for whatever stupid reason, caused a big mess I would think. [yeah, that's right]

M: Have you ever heard of a researcher named Naranjo? [no] He did an algorithm to help clinicians assign causality and I have it here and I was just wondering if you could take a look over it and see if there is anything, any of those questions that you feel are not relevant to the Phase I oncology clinical trial setting. And then you can just cross out any that you don't feel are relevant.

S14: That are not relevant? [yeah] Are there any previous conclusive reports on this reaction? That's certainly relevant. I would say two questions would be less, less important for me. [okay, which one's?] Whether the drug was detected in the blood in concentrations known to be toxic. [okay, why?] Well we talk about a Phase I situation so you can have unusual reactions to, to unusual drug levels. So I would, I would take that into account but I would not put my judgment on it and say you know, the concentration was very small, we should not do that. I've seen patients reacting in weird ways to drug levels that we thought would be completely safe. [right] So that would be something that I would be very cautious about. And the same applies to, was the reaction more severe when the dose was increased or less severe when the dose was decreased? [okay] We sometimes, in Phase I studies you can see reactions just happening to the same extent regardless. Just because the patient is exposed to the drug, it does not necessarily have a [not necessarily a dose-response] a dose-response relationship. So those two questions I would certainly, they're relatively important, but the others are good questions. And that's what we usually try to rely on, are there previous reports?, is there a timely relationship between drug and reaction? If you re-expose the patient do they have the same?, I just had two patients with

this, where we, one of the patients we did not re-expose him because the situation was too severe. Another patient insisted on continuing and we did and so far it did not re-appear. But I have still do not have a good explanation why he did have the adverse event in the first place. So but yeah.

M: So would you be able to rank the, so you're crossing out 7 and 8.

S14: I would not cross it out I would just not put that, not as much emphasis as on the others. [oh I see, so those would be less important] yeah, yeah.

S14: I mean, clearly one of the most important questions is if you have similar reports on this drug in similar situations. [yeah] I mean that's the first thing you look at, is this a known side effect?

M: How would you, how do you figure that out? [what do you mean?] How do you know if there has been previous reports of that reaction like that? What resources do you refer to?

S14: Well, investigators brochure [yeah] current literature um, personal communication with other investigators, the whole nine yards. Sometimes if you have other drugs from the same class of drugs which are further developed you can at least try to make a cross conclusion if there is a class effect.

M: Now you said you personally communicate with other doctors, is that usually other doctors here at the site or do you [no no] talk to other investigators?

S14: Other investigators who participate in the study [in the trial] or have experience with these kinds of drugs. That's not restricted to the centre, [okay] we live in a very global world. [you would just give them a call and say, have you ever seen?] Phone call, email.

M: Are there any questions on this list that weren't there that maybe should have been?

S14: Not anything obvious. I think, I think it pretty much has the, the 10 questions that you usually go through in your head when you try to assess causality.

M: Do you think something like this would be useful [yeah] if it was implemented more widely?

S14: Yeah, you would certainly not miss anything and you would have a constant reminder what kind of points you have to, to tick off.

M: So now I would just like to ask you a little bit about your experience as a clinical trials researcher, we're almost done. In which cancers do you specialize?

S14: Gastrointestinal, genitourinary.

M: What year did you receive your MD?

S14: In Germany [what year was that?] oh, 1993

M: And do you have a Masters or a PhD or anything?

S14: No.

M: What year did you receive your oncology license?

S14: When? [yeah, laughter] 2002

M: What year did you become involved as a clinical trials researcher? [sorry?]
What year did you become involved as a clinical trials researcher?

S14: That would be 1997.

M: You didn't have your license until 2002?

S14: That's the German system. You start, we have a six-year internal medicine residency program and then a two-four year combined hematology/oncology fellowship program. [oh okay] And it's not a program like here where you, like a two-year fellowship and then you get kicked out, it works a little differently. [right] And you have one or two year leeway doing exams, sit your board exams or not. [right] But in Germany you start doing clinical research basically doing your residency. So in 1997 I started a residency position at a university hospital and got involved with clinical trials. [okay] So that's the difference.

M: Do you have any other certification then to do with clinical trials or any other?

S14: What do you mean qualifications?

M: Like any other certifications, any other course work or any education around clinical trials.

S14: Yeah, I have, I, I, I ah, did a training to, for, for clinical trials physicians in Germany. It's a course you have to take, contains all the different aspects of clinical trials, ethics, data monitoring, whatever you need, GCP and regulation things. [okay] So I'm, so I have basically a certificate of attendance.

M: Good, and what year was that.

S14: That was in, around 2000.

M: So overall, what percentage of your work time would you say is devoted to anything to do with clinical trials?

S14: Anything to do with clinical trials? [yeah, even writing protocols or whatever] Physican working hours [yeah] or all of the working hours? [laughter] I would say it's probably, right now [yeah] maybe 80/20 [80% trials?] no, no, 20 [20% trials] just because we have a big chunk of regular clinical work so.

M: And then of that 20%, what percentage is devoted to Phase I and II trials.

S14: So 20% would be a day a week, yeah 70/30, I would say 70/30.

M: And of that 30% what percentage is devoted to Phase I, Phase II trials as opposed to Phase III.

S14: 80 [80%] at least 80% is Phase I/II [and 20% to Phase III]

M: And have you ever been a local PI? [yeah]

M: Can you tell me about any training that you received specifically with respect to assigning causality to adverse events?

S14: You mean overall or specifically for trial.

M: Specifically on

S14: Because I did receive the training as a clinical trials doctor, which had some training in there for assigning causality. But otherwise I've never received I think formal training for assigning causality.

M: What additional education do you think should be made available about assigning causality to clinicians?

S14: I think a training tool would be helpful, especially if you start in a clinic like this, I imagine it would certainly be helpful for, [so if you are just starting out] junior, junior staff members who just start in this field.

M: What would that look like?

S14: I think it gives an overview of what the different categories are [when you say categories you mean probable, possible?] yeah. And what, what kind of assays fall into the different categories and then it probably should contain a fair number of samples and examples. And then something like the questions you showed me, something like this. [okay, great]

M: What do you think would be the best way to implement something like that, what would be, web-based or CD Rom or lecture, workshop?

S14: Web-based [yeah] A workshop you have to get together and probably not a day filling thing, it's probably a couple of hours or so. So I think a web-based thing would be the best, like the Ethics Course you have to take.[oh the ethics course like the NCIC ethics?] Yeah, it's web-based too and you just sit and you get, you get the explanations on the way through the, through the [great]

M: Well I think that's all the questions I had for you today. Do you have any more questions for me?

S14: No, let me know about the outcome.

Subject 15

M: So what we're looking at doing is, we want to know a little bit about the decision making or the rationale that goes or the reasoning that goes behind

physicians assigning causality to adverse events that occurred, specifically Phase I clinical trials. The reason we are interested in this is we want to see if there is a need for a tool or some way to systematize that process a little bit better. And um, just want to talk a little bit about those, those issues. Even the most experienced clinicians find assigning causality to adverse events challenging. And sponsors, clinical trial cooperative groups, research ethics boards they all expect prompt and sensible causality assessments. But I'm sure as you know, it's not always that easy or straightforward and if done poorly can have some implications. So we're interested, like I said in developing a tool to help clinicians make assigning causality a little bit more reliable. We feel that by better understanding your needs as a clinician we can make the tool more relevant to you. [mmm hmm] So do you have any questions [no] about what we're doing? [no, that's pretty clear] Okay, good. So first of all let's just say one of your Phase I clinical trial participants reports experiencing an adverse event, let's say it's a serious adverse event. Can you walk me through that situation, how that situation is handled?

S15: How that situation is handled? [yeah] Well it can present itself in a number of different ways, number 1) a patient can phone in to say that they're having this problem. And based on what they tell us over the phone in terms of what they're experiencing we might ask them to come in to be assessed. [okay] So once they're, when they are assessed, basically it's the patient describing what's going on and, and what they're what they're presenting with in terms of symptoms, vital signs, lab test results. We look at everything and then we make a decision on the severity of what the patient is experiencing. [okay, yeah] So an SAE is a patient being admitted to hospital, so it might, it's, it's severe in the sense that it's reported as an SAE because they are admitted to hospital. And so usually an admission to hospital is usually at least a grade 3 or 4 that we would admit them for. And in terms of how we decide whether they're, a physician makes that decision to admit and assigning causal, ah relationship or severity. We use the common toxicity criteria for assigning the severity. Causality, whether it's the

drug, you take into consideration the patient's past history. It maybe a symptom that they were having before that was poorly controlled. For example, if it's their, their pain, it could be maybe that their disease is progressing or it could be because of the medication that's causing it. [okay]

M: So you look at other factors like whether it's the progression of their disease.

S15: Well it could be their disease, it could be you know, you have to take everything [beeper] you take everything into consideration. You take everything into consideration, you have to put everything together, it's not just necessarily the patients symptoms, you have to look at their lab values, look at their medications they're on, what's, what's causing the problem. **(a lot of work)**

M: So now do you actually do the assigning of causality or how does that work?

S15: It's basically a, an investigator, I mean I'm a nurse, I'm oncology trained, I have lots of experience, giving chemotherapy and looking after patients who are on chemotherapy. Lot of experience in looking after different types of patients, cancer patients, so you know, my experience does help in, in terms of identifying whether it is related to the drug or not. That's part of my job to know what the side effects are or potential side effects are of the medication. If it's combined treatment, I know what the side effects of chemotherapy are but um, and you know what the expected, potentially what the side effects are of this new drug because of the type that it is. So a lot of it has to do with um, knowing the drug and what potentially could be a problem. But really it is the physician's responsibility to assign causality. [okay]

M: Do you sort of give him, this is my opinion and then he'll sort of say yes or no, I think you're right or well, let's look at this further or you know.

S15: Um, it's kind of a, you know really it is the physician and I might ask the question because I want to know or you know, just for my own benefit in terms of becoming more acquainted in the drug, I'll ask more questions [yeah] about why you think it is, why it isn't. Try to figure out what their rationale is just because down the road that will help me to better assess other patients that come along as well. [right, okay] But it's usually kind of, I mean not necessarily obvious but you know, you get to know the patient pretty well so if it's something totally way out of left field that's happened and quite surprising and there's no real other explanation for it because you kind of try and figure out, okay, is there another explanation for why this patient is experiencing this certain symptom. And um, you know, you kind of rule out everything else before you kind of point the finger. [could you turn that off just so I can answer this pager?] **(process of elimination)**

M: So what are the resources you refer to when you're assigning causality, when you're looking at when you're assessing the patient and those factors?

S15: Um, I will, one of the resources that I use we have on our computer, it's called, Up to Date. So basically if a patient is on some medication that I'm not familiar with I might look it up to see what the side effects of that particular medication is, is that the patient's on to see if maybe it's because of the new dose that we've prescribed for him.

M: Now does that include investigational drugs too from the database? [no, not investigational] So sort of like a CPS?

S15: Yeah, it's more than a CPS, it even talks about, like if there's a condition that a patient has, say they've got some weird, let's say they've got Lupus as well. I might look that, because I'm not familiar with it. I might look it up to see what symptoms the patient might experience if they had an exacerbation of their disease just to see if maybe that's what's happening with the patient. [so it has

information about diseases and drugs?] Diseases and drugs yeah. I'll use that as a source and then of course I use the protocol um, as a source of information in terms of side effects and [how helpful is the protocol usually?] um, it's helpful enough for me that. Um, like there will be a red flag in the um, in terms of the pre-clinical and clinical, initial clinical experience that they have with the drug in patients so it is helpful to me that way. I know that there is an investigator brochure which has more detailed information and in my particular role I don't have time to read the investigator brochure. [okay] So, but that would be the PI would, the PI knows more because they do read the investigator brochure about the drugs and potential, potential side effects. But um, yeah, with an investigational new drug, I mean lots of times you just don't know. I mean if a patient walks in and their LFT's are you know, they've been throwing up and you look and their LFT's are totally out of whack. And they were perfectly normal 10 days ago before they had the investigational drug and there's no other reason for, you know, they didn't go on a drinking binge, don't have a history of liver disease, then you pretty much know that the drug has probably caused, you have to assume it was the drug that caused that problem.

M: When you're looking at this whole causality question are there any tools that you use, algorithm, flow chart? [no] I know when you're grading severity you've got the CTC guidelines, anything like that?

S15: No, not that I'm aware of, not that we use here that I'm aware of. **(No tool)**

M: Do you think that would be useful, something like that?

S15: Um, yeah, could be if it wasn't too cumbersome [okay] because you know that is the one thing about any of, it has to be, it has to be something that's easy to use. **(tool needs to be simple and easily accessible)**

M: Can you kind of explain, like too cumbersome how? Like what would, what's too cumbersome?

S15: Well if it's like an octopus, like at the end of the day if it looks like an octopus, that's too cumbersome. I prefer yes/no, yes/no kind of thing and you just kind of very logically follow it through then that, that would be helpful to me.
[okay]

M: And do you think something electronic or paper-based would be better?

S15: Um, it has to be easy to use in either way [just has to work well in your setting] yeah, mmm hmm.

M: And you use the computer a lot so.

S15: Yeah, use the computer a lot, not always easy to get at in clinic but we do use it a lot yeah, more so than I ever used to for sure. [yeah] yeah [but not in the clinic] In the clinic I do it's just hard to get to one, there's lots of computers it's just the matter of getting to one. [because you're sharing them] mmm hmm yeah.
[okay]

M: What do you think are some of the problems or challenges with assigning causality?

S15: Um, probably the sponsor wanting an answer right away of what the cause, because sometimes you don't know, it's hard to make a decision on one patient, like the first patient that presents. **(sponsor placed pressure on making a quick decision)** Especially if that particular patient has multiple problems and it's possible that it could be their disease or a component of their disease that's causing the symptom or the, the abnormal lab result. Um, as opposed to knowing for sure that it's, you know if a patient comes in and they're like you and me and

you give them a drug and all of a sudden they're sick and you've, you've just treated a perfectly healthy person. It's easy to say yes it was the drug because there's nothing in the patient's history since giving them the drug that made them sick this way. [right] But when you have a patient that has multiple problems, it's, it's harder to assign causality. Especially if it's happened in that one person and it's the first time you've seen it. [mmm hmm] You, you, so sometimes we have left that box blank you know for a couple of visits until we know for sure that it was the drug or wasn't.

M: And the sponsor's don't particularly like that.

S15: Well no, they, you know, for them, a possible, you know, any time you have an inkling it might be related you have to go with that possibly. So is it or isn't it you know? [mmm hmm]

M: But if there is any question you usually say possibly? [yeah]

M: What are your concerns about how clinicians currently assign causality?

S15: Um, I don't have any concerns really, it's all, you know, um, kind of logically thought out um, and reasonable.

M: You mentioned feeling the pressure from sponsors to provide a causality assessment quickly. What other external influences or pressures have you felt from third parties when it comes to?

S15: Well even the sponsor, that's kind of going over the top a bit, they don't really pressure you, but ah, there aren't any other pressures.

M: What do you think are the implications of assigning causality?

S15: Um, well, of assigning them poorly? It's either you under, or whatever event it was so you're compromising safety of future patients who might go on this treatment if you um, rule that it wasn't related to the drug. Or you might over, you know if you say that everything is related to the um, to the investigational drug then you're over, over rating it as to whether the drug is causing problems. So it's pretty serious. **(apprehensive about consequences of causality attributions)**

M: And so what does, how is that, if you're over scoring what are the, what's the potential ramifications of that?

S15: Well the potential ramifications of that is the drug might not go out to market and it might be a potentially legitimate drug. [okay] Because describe SAEs or have SAEs that might not really, that are manageable or might not really be 100% related to the drug. Especially if you pick a poor group of people who you know always get admitted for nausea and vomiting because they have a poor ECOG status. And it could be that they were just very poor patients initially to put on treatment. [mmm hmm]

M: So then from your perspective what would make assigning causality easier?

S15: Um, more information from the sponsor I guess in terms of um, side effects of the drug.

M: Do you think there needs to be more pre-clinical work done or? Or is it just that you're not getting the information?

S15: No, no, we're getting the information, I guess to get more information about the investigational drug would be more pre-clinical work. But at the same time I think that these drugs are put out there for in Phase I trials and it's reasonable to use them at that, and not to wait any longer. I mean just to give an answer I would say that [mmm hmm] but at the same time I think drugs that are going out

now for Phase I trials I think it's, the sooner you get it out to the patient in a Phase I study, the sooner it will get offered. **(the drug development process is rushed)**

M: Have you every heard of an algorithm, the Narjano algorithm, a researcher named Narjano and he's created an algorithm to help clinicians assign causality. You've never heard of anything like that? [never of heard of it, no] I was wondering if you wouldn't mind just looking over these questions and cross out any that you don't feel are relevant to the Phase I oncology clinical trial setting.

S15: So the ones that are not relevant. [yeah if there's any there you think are not relevant] And so now I have to assign a number, okay.

M: Yeah, and then the remaining ones if you could rank them from most important to least important.

S15: Oh, so I have to rank them like 10, 9,8, 1 [sure] 7, 6, oh that's going to be tough, this is going to take a long time.

M: That's okay, there's no right or wrong answer and it doesn't, you don't have to over analyze it, just whatever you think.

S15: Yeah, because these are all kind of inter-related, yeah okay.

M: You can, if you know think some are the same, of the same importance you can give them the same number. We just want to get a sense of what you feel are the most important factors when you're assigning causality. [okay] Great, thanks. Good. So the most important was whether there were previous conclusive reports on the reaction. And the least important was #6 Did the reaction reappear when a placebo was given? [mmm hmm] Okay, great.

S15: I picked that last one because if it's a Phase I study you don't often get placebo.

M: Exactly yeah, some people have crossed it off just because it doesn't really apply in the Phase I setting. Now is there anything here, like was there anything that came to mind that you thought oh, something should be on here that wasn't, any questions that, things you think about that weren't included here?

S15: No none that came to mind but I thought they were very applicable questions, yeah.

M: One of our thoughts was that we might just try to modify this Narjano algorithm to try to make it more suitable for [yeah] the Phase I oncology clinical trials setting. Do you think this is too cumbersome, like you mentioned.

S15: No, no, they were, yeah, they totally made sense in relation to these I trials yeah.

M: And you think it might be helpful in sort of systematizing you know the process and making sure that you know.

S15: Well basically like all of those things we do consider [yeah] it's you know, they're very applicable to Phase I studies. I mean we don't really think that that's what we're doing but when I was reading them all I was thinking oh yeah, that is what we do when we're assigning causality.

M: Lastly I would just like to ask you a little bit about your background as a clinical trials researcher. So which cancers do you specialize in, all of them in Phase I?

S15: Yeah, pretty much. In Phase I it's any tumor site, so ovarian, lung, breast, prostate, GI, it's pretty much everything, melanoma, it's everything [head and neck?] head and neck, everything. [wow, everything] GU is my primary, so basically I do GU and Phase I trials so those are my two, two areas that I work in.

M: And do you have a Bachelor's in Nursing? [yes] And where, what year did you receive your Bachelor's in Nursing?

S15: In 1989. I'm also a certified oncology nurse.

M: Oh CANO, you have a CANO certification? [yeah] and what year did you get that?

S15: The first year, was it 95 or 96 it was the first year that they did the CANO oncology nursing certification. Yes, you can write 95, 95 or 96 I can't remember when.

M: And when did you get your RN license, was that in

S15: 79

M: Oh 79 okay, so you also have a diploma then in nursing.

S15: Yeah as well, yeah I also have a diploma that when I graduated in 79 and then I went back to university [oh good] and graduated from University in 89 [oh good for you okay]

M: And do you have any other like Masters, any other clinical trials training?

S15: I have, yeah, I was, I've let my certification lapse but I was, I did have my SOCRA CCRP, certification, it's the clinical, oh gee, research, Certified Clinical Research Professional.

M: Okay and what year did you get that? [1999]

M: What year did you become involved as a clinical trials researcher?

S15: 97. [1997 okay] mmm hmm

M: Overall, what percentage of your work time would you say is devoted to clinical trials?

S15: 100% [100%] yeah.

M: And then of that, what percentage is devoted to working on Phase I and II trials?

S15: Oh, Phase I and Phase II? [yeah] oh 100% [so no Phase III?] That's because I don't have any Phase III trials, [You're the specialists].

M: Can you tell me about any training you've received, specifically with respect to assigning causality to adverse events?

S15: On the job training. **(no formal training)**

M: On the job, from other nurses, investigators?

S15: Um, mostly the investigators.

M: What additional education do you think should be made available to clinical trial nurses?

S15: If there was an assigning causality course out there that would be helpful. Um, probably some, I don't know, you know, there's not much out there because clinical trials is kind of a narrow. I go to um, I go to our medical oncology rounds and basically I just kind of learn about new drugs and upcoming drugs just from attending medical rounds, just learning about what's up and coming. But yes, in terms of

M: You've been doing this awhile now but do you think maybe something earlier on when you were just starting to try and figure out this whole clinical trial thing might have been helpful?

S15: Well it's kind of hard to say because when I started working on clinical trials were very different then they are now.

M: Okay, how so?

S15: In just terms of the severity of patients that you're seeing and the type, the types of drugs that are out there now are much more complex than the ones that were there when I first started working in clinical trials. It was a much simpler life back then. **(clinical trials have become more complicated)**

M: Patients you are seeing now are a lot more complex because they've got additional co-morbidities and that sort of thing?

S15: They've usually been multiply treated with you know, yeah, they've had multiple treatments as opposed to when I first started working [oh you mean now they're on to 3rd line therapy] yeah, 4th, 5th, 6th line. Just the types of drugs that are out there now is significantly different than the types of drugs in terms of the

family that they come from [they're more targeted therapies] exactly, so that's really changed.

M: And um, with respect to education around causality do you think it might be worthwhile to sort of include a module or, maybe in your, what about in your CANO, that's not specifically clinical trials though is it?

S15: No it's not. You know you could do something like with NCIC but um, I mean if there was, even like a self-learning module that would, yeah, that would be helpful.

M: I think that's all the questions that I have for you [okay]. Have you got any additional questions for me. [no]

Subject 16

M: Even the most experienced clinicians find assigning causality to adverse events challenging. Many groups such as industry sponsors, clinical trial cooperative groups, research ethics boards they all expect prompt and sensible causality assessments. But I'm sure as you know, it's not always [mmm hmm] that straightforward and if done poorly there's implications. So we're interested in developing a tool to help clinicians more efficiently and reliably assign causality to Phase I oncology clinical trials. We feel that by better understanding your needs as a clinician we can make the tool more relevant to you. So do you have any questions? [no I don't] Okay, I will just start by asking you, let's just say one of your Phase I patients reports experiencing an adverse event, let's say it's a serious adverse event. Can you just walk me through how that situation is handled?

S16: Well if the patient let's say, there are different kinds of things, if the patient phones in, the patient would phone the nurse, who is a clinical trials nurse we would then see the patient, we would then assess them. Let's say it's a serious adverse event and we are going to then admit them and fill out the CRF's you

know and putting something in. [and what about] Alternatively they might present to an emergency room, so they might present to an emergency room with a serious adverse event and then we get called by the emergency room. How do we assign causality? [mmm hmm] I think that's interesting, because there are different issues around assigning causality. The first issue is how quickly can you really assign it? Often you know, you need to report within 24 hours. Within 24 hours you may report, the person came in with chest pain, da, da, da, and you don't have any real idea if it's related or not. The second issue is deciding if they're on a chronic therapy, do you continue drug or not? Because if this isn't drug related then you may continue drug, if this is drug related then you don't. Generally in most Phase Is regardless of whether you think it's related or not you would stop drug, you know, if it's chronic dosing. The third issue around this serious adverse event is sometimes you know, if it is a life threatening event is, there you have somebody on a clinical trial where most of the time in Phase Is they're in cancer patients, they're end stage patients you know, in that they don't have curable disease, you wouldn't go to heroic measures often. Yet in the face of the Phase I you may want to do more heroic measures than not. And this can become a problem in the night or on the weekends if the person who most understands the trial is not around for those decisions. So there's also the decision-making around causality of, you know, you want to keep that person alive because number 1, if it's related to drug and iatrogenic or whatever then you want to try to get them over that because you might have caused this. Number two, if it's related to drug you want to see if you could reverse it because you might learn more about the drug. Um, number three, if you do, do heroic measures you might also be able to further establish is this due to drug or not? So then I think you get into this whole situation too of assigning causality to make those decisions. Having said that if this is a person with widespread metastatic disease it might not be appropriate to do very heroic measures. So you're in a bit of a bind so you want to be able to quickly assign causality. If it clearly is a 78 year old guy who, that man up there was in a Phase I, that guy who's standing in the white suit. He was on a Phase I study and he had a massive heart attack,

Phase 1 study. [right] And um, on the one hand was it just due to a heart attack, due to being an elderly guy, in which case, it wasn't a bad escape for a guy with metastatic cancer. On the other hand if it was a heart attack due to the drug I was giving him then maybe it wasn't a good end. [right] I mean I think it's a difficult area. I'm going around in circles. How do I assign causality? I usually assign causality by looking at the symptom, is it something that could be expected from the class of drugs that we're looking at? Is it something we've already seen in the trial? Is it something that's coming on a temporal basis where it could be unusual? So I think the first thing is that if it is something that's already been seen in the trial, if it looks like it it's temporally related, if it's something that could be expected then I think that, although it might be definite, their white counts have fallen and they're septic definite. More often you might not assign as a 5 you might assign it a 4 as probably or a 3 as possibly, you know [mmm hmm] in terms of that. I think if it's a brand new symptom, particularly if it's a first in man drug, a brand new symptom that you don't have any expectation of and that you can't necessarily relate to temporally. Let's say it's a three-week schedule and this is on day 8 or day 10, it's not necessarily predicted, I think it's very, very difficult and I think there's two big concerns. One is if you assign causality and say it's related improperly then it might tarnish a good drug and stop dose escalation in a way that wouldn't be appropriate. Alternatively if you ignore it, it might cause further toxicities in others and be potentially dangerous to other patients. I think it's a very dangerous thing. I also think that sometimes as oncologists we tend to minimize rather than maximize because we're used to toxicity with drugs and that can be dangerous. **(err on the side of caution)**

M: Can you give me an example of when you've seen that?

S16: Well I think even neutropenia you know, low white counts, we can deal with low white counts, so we ignore things like that often. I think we get used to dealing with that neuropathy in some drugs. I think that we would rather have a drug that works and deal with toxicity. So that in a Phase I you often don't know if

the drug works but I think you're going to accept a reasonable amount of toxicity. I also think it behooves us, often in cancer centers we don't have all the facilities necessarily right at hand to characterize. So you know, if indeed you get cardiac toxicity, you're not an intensive cardiac unit and how many of our patients would be accepted to it? And that's where the heroic measures come in because you know, it may be that we need to have them accepted to an intensive cardiac unit to assess if there is really cardiac damage in a way that's much more rigorous than we might assess cardiac damage in the cancer hospital where we're not assessing cardiac damage, you know, it's a different level. [phone rings] Does that get to you what you wanted? [yeah, yeah that's, that's great, so what about] So how do you assign causality? I think you assign causality by number 1, looking at is it something expected?, number 2, is it temporally related?, number 3, is there any possible way, erring more on the side of ... You know, number 4, is it something that was related to a pre-existing condition or is there something obvious that can explain it? And finally erring more on the side of assigning causality to drug than not because it's the safer way to go.[right]

M: And what do you think are the implications then of assigning causality? You mentioned earlier

S16: I think one poor, I think one problem is if you have too many DLT's, you can stop dose escalation in a Phase I drug and maybe kill a good drug because you [54]

M: Have you [55] can you give me an example?

S16: Well it's hard to know because you never know if they were going to be a good drug, okay? [yeah] you know? I think there's situations where dose escalation has stopped but you know, you can't really say it was a good drug because you don't know because you've never gotten there. But I think there are sometimes you know where you stop drug development. [okay] And you know,

one example, it's an old example but you know, you even look at Taxol, first Phase I study of Taxol had some doubts and then it took them a couple of years before they were able to figure how to give it. And you know Taxol has been widely used since then. Now they did eventually figure out you know, and the causality was true that it was due to hypersensitivity but it did stop the development of the drug for a couple of years and in another situation they might not have gone back to it. [right]

M: Do you use any tools to help you when you're assigning causality or do you think decision trees, algorithms of something like that would be useful?

S16: Um, possibly as a training mechanism, you know, sort of going through if this, then ... you know, it could possibly but. You know, most of the time you have to do this fairly quickly, it's not like a teaching tool. So it could be helpful in terms of teaching residents how to think about things, but I don't think you'd use it in the real world. It could be helpful to teach nurses how to think about it. Ultimately it's almost an intuitive sense of you know is this related? **(doesn't think a causality assessment tool is applicable in oncology clinical trials)**

M: What are your concerns about the way in which clinicians currently assign causality?

S16: I think sometimes, sometimes you're in such a rush to get the CRF done that I think you don't necessarily spend enough time. And I think one of the other problems is we get so many reports about drugs, you know like alerts [safety letters?] safety letters that sometimes everybody doesn't know these things and may not know if it's related or not. I think keeping up with the safety letters is hard, [just because you get so many of them?] mmm hmm and not really knowing the drug well.

M: A mentioned something about you guys had developed some sort of a system for safety letters [mmm hmm] can you describe that for me?

S16: What we were trying, we do everything electronically. What we do is we have a Phase I ah, meeting every two weeks and what we try to do at those Phase I meetings is talk about the recent alerts. And one person, the PI that would be assigned for that safety alert but we would then summarize it say, once every two weeks for all the Phase I docs so that everyone is up to date. Because like if A is the Phase I doctor and there are 4 other people working with him, he's the only one that gets those safety letters so how do the other 4 people know about them? **(lack of communication between clinical trials staff)**

M: So do you have them all in a database [mmm hmm] that's made available to all the other investigators on the trial or?

S16: Well yeah, we're setting that, we actually don't have the database set up, well there is a database you can go to but we're setting up an easy database [oh, okay] so there will be an itemized thing. So let's say I'm doing a study of drug X, we've talked about it let's say at the meeting but as well as talking about it, let's say I've just come in as a new nurse on the trial and somebody comes in with cough. I can go there and I can look up and oh at Hamilton there was a cough reported and in another study in New York there was a cough reported. I could go back and you know, or I might look it up and say oh well there's been no alerts about this and there's been no dose-limiting toxicity at all and no serious adverse events on this drug. I might say I don't have anything to help me with the cough you know. You'll be able to go back, ploughing through the whole thing. So what there is going to be is just a, a grid, so there would just be a grid. So let's say for Phase I, X you know, you know X, there would be a grid saying you know, 05 November, cough, grade 3 you know [right] 06 February you know, neutropenia, 06 March neutropenia and then I'd be 06 June, oh you know I've got another cough so that's, I'm going to put in something you know. I can look back

and say well cough has already been reported with this drug. It wouldn't have a lot, it would just have you know, and then, and then it would be linked so that you could then go to the link and you could go to the safety alert thing that's on the, if you wanted to. [oh, I see] So if I said cough, I wonder if that cough is similar to the cough that I'm seeing today, I could then you know click on the thing, I would get into the safety alert letter from the drug company. Unproductive cough coming on, you know treatment dah, dah, dah, oh and I'd say that's exactly like what I'm seeing.

M: Okay, so when you receive the paper-based letter from the company you scan it in [yeah, mmm hmm] somehow? okay, I see.

S16: We do it, well we ask for everything electronically [oh I see, so the company is sending it to you electronically?] they are starting to send it yeah, otherwise we scan them in yeah. Because otherwise you wouldn't know you know? [yeah, yeah]

M: And you use that in conjunction with the investigator brochure [mmm hmm] right? [mmm hmm].

S16: Well the investigator brochure isn't, isn't updated regularly. [yeah, ah ha, twice a year or something right?] mmm hmm. **(IB not always reliable, not up to date)**

M: What would you say are some of the problems or challenges of assigning causality?

S16: We've been through those, I think I already said. Challenge is figuring out if it really is related or if it's due to underlying disease of the patient. If it's brand new, I'm figuring out you know, it doesn't make sense to be related to the drug. [so when you say] And doing it on a tight, tight time schedule. And also

sometimes doing it without the benefit of all the fancy investigations that you might have related to that site of disease. So that's what I said, we're in a cancer hospital so if someone comes in and tells me they've got chest pain, it's not like I'm in the middle of a cardiac centre. So then I have to send my person over for a cardiac assessment but meanwhile the drug company wants me to assign causality within 24 hours. The other challenge is if they go to a different hospital and making sure all the right tests have been done. Often we're assigning causality in a bit of a void because we haven't necessarily sent the patient right then. You know, as a PI you're asked to but let's say it's a Saturday and they went to another hospital, you know. [yeah] Or the resident saw them, you know, you're assigning causality without necessarily having been right there.

M: What external influences or pressures do you feel from third parties? You said the timeline factor.

S16: The timeline, it's mainly the timeline and the pharmaceutical company.

M: Any other influences or pressures?

S16: I think one could say the IRB is going to be a pressure but I don't think it really is, it's a good pressure.

M: What's their pressure?

S16: Well just to make sure you're following all the rules that you said you would with Health Canada or what have you. I guess the only other pressure would be you know making sure you can book all the tests you need to get booked.

M: Right, so that comes down to availability of health services? [Exactly]

M: So from your perspective then what would make assigning causality easier?

S16: I think tools like having all the previously known side effects of the drug readily available. I think that's the biggest tool [like your database that you're developing?]. Yeah, yeah, I think the second thing is being able to prioritize Phase I early drug patients for extra testing if you them, like if you need a heart scan or you need something you are able to get those done in a timely fashion. And I think the third thing is, always having more time for all these things is the other thing, but the third thing is being able to possibly inform the company as to the procedure. So we first inform them that something's going on, we do this sometimes you know, we're investigating it but don't have to assume final causality until [8:52] which we do but it's a lot more paperwork. So they want a causality right away so you might say probable and then fill out another form and you say no it's not related. And they say well I want 5 forms on why did you said probable before and now you say not? [Yeah, more streamlined 9:08] Yeah, a little more fluid. **(changing your causality attribution creates extra work and issues with pharmaceutical companies)**

M: Do you have any,, do you have any initiatives underway right now in terms of prioritizing those Phase I patients so that they can get to those tests?

S16: Well we try to do it but you know, it's not a formal system but it's [9:25]

M: Now um, what about in terms the way causality is graded because I know that [the 5 grading?] well you're mentioning 5, now which grading scale are you referring to?

S16: Well the one we usually use is, I don't remember what the name of it is but I thought it was from NCIC, definite is 5, probable is 4, possible is 3, probably not I think is 2 and not, definitely not is 1. I think that's what we tend to use. The other one is a four one which is not, possible, probable, definite. I think we tend, most of our studies are 5.

M: Because I've noticed it seems to vary depending on the study and what's sort of outlined in the protocol.

S16: So it would be nice if there was one. I think actually you know, I think definite, probably, possible are the three that are most important, and not are the three, are the four that are most important. When can you say definite? You can't say definite sometimes, probable is better some of the time, you know. Then when you're writing up a paper or looking at assigning, you know possible is in this grey zone. But I think it's very hard with a Phase I study to say definitely not, there are lots of possibles where you want to have that scale though.

M: What do you understand possible to mean?

S16: I understand possible to mean that there are a lot of other factors that I can't assign it, but that I can't totally rule it out. So if I said, if I did a cough and I said possible and this woman had no other factors, got this drug, possible. And then you know, the next patient in Montreal had a cough and then somebody in Hamilton had a cough. We could then say no, the Hamilton one by then A might assign probable to it. But it's a fluid, it's an evolving thing. So we just had a study where a drug, it was an NCIC early Phase II study where a drug caused pneumonitis and it wasn't picked up by the first few. A number of people had cough and a number of people had pneumonitis and it didn't get picked up. Although this class of drug could cause, the parent drug could cause pneumonitis, the next drug that was developed didn't really cause a lot of pneumonitis and we had more experience with that and this was a new drug, a newish drug which hadn't been reported to cause pneumonitis. So the first few were possibles, possibles and now when we see one it's a probable or a definite. So it's, it's got to be fluid. Now should we go back? yes, in our database at NCIC we've gone back and reviewed those ones that were possible and now have made a lot of them you know, probable. But at the time, at the moment when this

causality was being assigned you couldn't say it was probable. So that's what I understand by possible.

M: Are you familiar with the algorithm that was created by Narjano [no] to help clinicians assign causality? [no] Okay, this is it and it's a series of 10 questions and I guess what I'd like you to do is if you wouldn't mind having a read over those 10 questions and then cross out any that you don't feel are relevant to the Phase I oncology clinical trial setting.

S16: Um, Phase I, I don't think placebo is you know. So should I just do an X on the side here [well just cross it right out, that's great] I think most of these we wouldn't have, I think for Phase I, already previous, that's important, did the adverse appear after, that's important, improved when discontinued but not usually possible, causality usually needs to be considered earlier you know [you have to make a call] than a washout you know. Alternative can cause reaction, yeah, was the drug detected in blood, usually do not have enough pk data to be useful, so you know, detected in blood and then we usually don't have the pk data and then usually only decrease dose per patient. And then we have to rank them? [yeah just sort of] Most important okay. [yeah most important would be 10] So are they, that would be a 9 I think, now did you want them [no that's fine].

M: And the one that's the lowest that you ranked was number 3, did the adverse reaction improve when the drug was discontinued.

S16: Usually we don't have an antagonist, and discontinue, I don't think we usually have enough time for that I think we're assessing causality before that you know [yeah, excellent] okay.

M: So I guess the thought was that we might try to modify something like this [mmm hmm] for use as a [yeah, yeah, good] Whether it be for a training tool or [or whatever yeah]

M: Lastly I would just like to ask you a little bit about your experience as a clinical trials researcher. So you're the head of the IND program here right [yeah] and what cancers do you specialize in?

S16: Breast cancer these days, I do HIV, some HIV malignancies and I do Phase I and breast. So I see everything with Phase 1.

M: So what year did you receive your MD then?

S16: 79

M: And what year did you receive your medical oncology license?

S16: 84 [84]

M: And do you have any other clinical trials, do you have a Masters or PhD?

S16: No, I did the work in England, the training in England. [clinical trials training?] mmm hmm. [when was that] Oh, 88 and 89.

Phone rings

Subject 17

M: Even the most experienced clinicians find assigning causality to adverse events challenging. Many groups such as industry sponsors, clinical trial cooperative groups, research ethics boards they all expect prompt and sensible causality assessments. But I'm sure as you know, assigning causality isn't always that straightforward and if done poorly there are implications. So we're interested in developing a tool that will help clinicians assign causality in the early Phase I oncology clinical trials. We feel that by better understanding your needs as a clinician, we can make the tool more relevant to you, to clinicians. So do you have any questions then about what it is that we're doing before we start?

[no] No, okay great. So let's just say one of your Phase I clinical trial patient has just experienced an adverse event, a serious adverse event. Could you just walk me through how you assign causality in that situation?

S17: Well typically it depends on the disease the patient has and typically in Phase I studies the patient has advanced disease in the cancer research milieu. Because that may have a direct effect on whatever problem they're experiencing. So the immediate question is always is this a disease related event or is it a drug related event? Or is it something completely unrelated to either disease or drug and perhaps to some other underlying medical condition? I typically will base my opinion on a combination of patient's history regarding this particular symptom, their, their examination in terms of confirming the nature of the problem and any relevant laboratory work. And then I will pause and reflect and think about what is the likeliest thing to be going on. **(takes time to reflect on the situation)** Very frequently in Phase I studies one tends to attribute any adverse outcome to the investigational drug or a combination of the investigational drug with other conventional treatment which maybe ongoing as part of the cancer treatment plan. exam, lab tests and basing the decision on your understanding of And only attributed to disease if it is very evident that the patient is having say a rapid progression. So the sort of examples might be, if a patient with bone mets from breast cancer on a Phase I trial gets started on a drug yesterday but comes in with a fractured femur today which has broken through a large lytic lesion I will very clearly attribute that to disease because there is no way the drug could have done that kind of damage. On the other hand if the patient comes in febrile and septic or they come in with respiratory problems where they previously had none, I would be inclined to attribute that either to the drug per se or as probably attributable to the drug because we've always got a gradation. [mmm hmm] Is this definitely attributable or is probably or possibly attributable on the scale? So one errs on the side of caution in that you do not want to underestimate the risk that the drug might have caused an adverse event. So it's very much based on gathering the knowledge from as I said, patient history, patient their disease and

their drug and the balance of probabilities, which is a qualitative assessment as to whether you think the drug is responsible. Frequently it's clear-cut and sometimes it isn't. [mmm hmm]

M: And you said that um, it's a balance of probabilities [yeah] but that's qualitative [yes] rather than quantitative.

S17: Yeah, the quantitative elements factor in, but in the end you have to make a judgment based on probable distribution of risk. And whether you call that qualitative or quantitative I think there is a component of quantitative evaluation of the probability of the drug is responsible. But there is also some qualitative judgment based on your years of experience as a practitioner. More often than not we will attribute either definite causality or probable or possible causality to the drug if there is no other reasonable explanation. [right]

M: And how do you differentiate between probably and possibly and definitely, you know, what sort of?

S17: Sometimes it's difficult. I think a very good example might be a patient with advanced cancer has begun a Phase I drug and sometime later, it could be a week or several weeks later the patient gets the deep vein thrombosis and a pulmonary embolus. Now you know patients with advanced cancer have a high risk of getting those types of adverse events so you will classify it as an adverse event. I think when it comes down to assigning causality as to whether it's disease, I think you can only say that there's either a probable or possible relationship to the drug. You can't exclude there being a relationship but nor could one unequivocally assign the accountability to the investigational drug. [mmm hmm] **(rare and difficult to assign 'definitely')** And one only sorts out those sorts of questions when you eventually get to Phase III randomized trials where there will be adverse events in both groups and you are looking at the relative incidence [right] in both groups. [right] A classic example would be

hormone treatment for breast cancer. [right] I, I think most of the doctors who do a lot of clinical research are aware of the fact that you don't want to underestimate the toxicity of a drug. But at the same time you don't want to assign every single adverse event to the drug some will not be due to the drug. So you usually end up in the, this is a possible to probable consequence of the drug if it's in the grey area where there could be many reasons why the patient had an adverse event. **(apprehensive to make an attribution outside the grey area)**

M: What are your concerns about how clinicians currently, how they currently assign causality?

S17: I think the concern inevitably has to be consistency. For example, if you have a Phase I trial with multiple investigators or it's taking place in multiple sites their level of attribution of causality to the drug may vary between investigators. One always worries if an investigator who is on, perhaps working with a drug company may wish to minimize adverse events because they really want this drug to be a success or acceptable. And it need not necessarily be driven by egregious opportunities around receipt of research funds, it may be because they get sort of um, too invested in the drug itself and wanting it to succeed or wanting their career to succeed or something of that nature. But that can induce investigator bias. **(researcher bias is a concern)** Um, on the other hand you can have some investigators who um, will always attribute causality to the drug because they rather simplistically think if anything bad happens it must be the drug. Now an experienced investigator, and none of the people doing Phase I clinical trials are inexperienced, usually they are the most experienced, they are very unlikely to over attribute causality to the drug. Sometimes with Phase III trials where you've got inexperienced investigators who are born pessimists perhaps. So in reality there needs to be a dialogue between investigators about how they do it, or even a tool as you're discussing, as to how you try and do the attribution. [mmm hmm, mmm hmm] Internal consistency, that's what I mean

[right] not only, there has to be a reliable and reasonably accurate approach to consistency as well. You can be consistently bad at it [that's right] if you're not careful. [that's right, reliable but not valid right] That's right you could be consistently invalid [yeah] yes. **(consistency isn't always a good thing)**

M: What would you say are some of the problems or challenges with assigning causality?

S17: Um, the principal problem is the multi-factorial nature of the adverse events. In an ill population with advanced cancers to whom a number of adverse events would naturally accrue even if you didn't give them any treatment. So it's the difficulty in discriminating between disease versus drug. And this can be particularly the case if you see abnormal liver function tests, abnormal renal function, non, non-specific pulmonary infiltrates in patients who may have a predilection to become infected, which could be drug, could be disease, you know, I'm thinking of lymphoma, myeloma patients. The biggest difficulty is that sometimes it isn't clear and it never will be clear. **(there may never be a clear cut answer)** Sometimes it becomes clearer over a period of time when you do investigations and you finally give your best assessment. But these are all evaluations that take time to come to a reasonable conclusion. You may have, you may send in an immediate adverse event notification form because the patient is very sick today and you may not know why completely, but over the course of the next week or so you may have a much clearer idea and then you can further clarify that. But in reality it comes down to investigators conducting appropriate evaluations and appropriate management. **(first time management is mentioned)** And investigators having clinical expertise as well as being simply able to look at [9:07]. So you need a degree of balance analytical thought and you need a degree of [9:14].

M: What do you think would make assigning causality to make it easier then?

S17: It's not easy to make it easier. [laughter] I'm somewhat skeptical that this is going to get any easier and I'm not even completely convinced a tool will make it easier. But I would very much welcome any thoughtful presentation on making assignment easier. My sense is that if a tool is developed or any other strategy it should be a means of enhancing the dialogue between investigators. **(lack of communication)** Not only for a single study but between investigators who collaborate across a range of studies. [okay] Say at the National Cancer Institute of Canada level and so on. So it might need some high level thinking by the leaders in a clinical trials organization and some dialogue that perhaps could be based on a communication tool that would be a prompt to them in trying to define causality into different categories.

M: What do you sort of envision this communication, I know you're thinking, you're probably thinking this is best left to the higher ups in the, sponsors.

S17: Oh no, no I think um, in some ways one could evolve a tool that has some relationship to, for example the National Cancer Institute of Canada or other clinical trials toxicity criteria. So you could base it on toxicity criteria which are in well described categories, of you know, what do you call it performance status, renal, hepatic, pulmonary, those sorts of things. And you could potentially go through those and say well, under which circumstances are we likeliest to see adverse events in this category based on causality related to the drug? Under other circumstances are you likely to see them? In reality you would have a different assignment for different []. A communication tool that would address dialogue between investigators would be essentially helpful. But it could also be quite complicated. And a tool that would, facilitate the assignment at the time of the event I think will be quite challenging to design so I think it will be interesting to see what other people might come up with. [mmm] And it would have to be practical and useful to the clinicians in order to be greeted warmly by them. [mmm hmm, great] **(tool will not be readily accepted by clinicians)**

M: Given the choice, would you prefer to grade causality on a scale or as a yes related to the drug or no not related to the drug?

S17: You cannot possibly do it on a yes or no. A scale however shouldn't be a, I don't think a 1 to 10 scale is a good idea. The vast majority of causality assignments are on a scale and they usually are categorized as unrelated or related which is a yes or no and at least two in-between, so possibly and probably. And I'm very comfortable with that because I honestly do not think it's easy to get down to a much more detail than that. [mmm hmm] Plus it gets pretty hard to garner all that information as part of the reporting to ethics committees and to applications that come out of clinical trials. So about four categories is fine for me which is the type of modified scale. [mmm hmm]

M: Have you ever heard of an algorithm that was developed by a researcher named Narjano? [no] No, he's developed an algorithm to help clinicians assign causality and this is it here. I was wondering if you could just have a look over those questions [mmm hmm] and cross out any that you don't feel are relevant to the Phase I oncology clinical trial setting.

S17: Why would you want to know did the adverse event appear after the suspected drug was administered, there's no, we're not in the business of reporting events that occur before the drug is administered, that's stupid. That's okay. Any previous conclusive reports on this reaction? This is vague, reports on this patient or reports on this drug, that needs to be much more specific. [mmm hmm] Drug reports, patient reports, sloppy question. Um, did the adverse reaction reappear when the drug was readministered? That's highly relevant. Are there alternative causes that could have?, yes that's relevant. We do all this automatically. Did the reaction reappear when a placebo was given? It is not routinely giving a placebo to monitor for a reaction so this is impractical, might do it in certain at both ends. Was the drug detected in the blood in concentrations known to be toxic? This is occasionally helpful. Helpful but, I think it's not relevant

in a Phase I clinical trial because you don't know what a toxic dose level is. [right] I'll put a tick but I'll but dubious here. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? You're not going to be increasing the dose if you got a severe reaction. Are these severe reactions or not severe reactions? If it's trivial you might, for example, low white count, might not necessarily spur you to reduce the drug if you don't think it has an adverse effect on the white blood cell. So this is, this is probably relevant. Did the patient have a similar reaction to the same or similar drug in any previous exposure? This is not helpful in a Phase I setting, because really how many Phase I trials is any one patient going to do, or classes of the same drug? Now in the fuzzy wuzzy Phase I world of pretty harmless drugs for well volunteers is a different situation, which is why this was written. For example, there's a lot of healthy volunteers where you can try anti-depressant A for Phase I and they'll come back and you pay them some more money and they'll do anti-depressant B or analgesic. So they may have had a similar reaction in a similar class of drugs but truly on the oncology clinical trials and this says oncology here, I think it's unhelpful because you're not likely to be offering Phase Is in the same class to a variety of patients. [mmm hmm] And one rarely offers Phase Is in the cured patient setting or the well patient setting. Not that it's impossible but it's a rare event [yeah] in Phase Is. Was the adverse event confirmed?, yeah this has to be. So this is a pretty useless scale, I wouldn't put any investment into that one. [okay] The things that are ticked as yes you would automatically do, so that kind of thing is unhelpful. The things that are silly one would be horrified if one was asked to do them because they're a complete waste of your time. So that type of scale is useless. [okay, good, that's good feedback] I'd be interested to know after we finish this interview what everybody else thought of that scale. [laughter] But don't tell me now, it might prejudice the rest of my replies. [laughter]

M: So were there any questions on here that you felt, you know, in a tool similar to this were there questions that maybe should be on here but weren't?

S17: Yeah, lots of questions, poor tool, weak, important questions left out. And I'm not going to try and design it for you because it would take me too much time. So the sort of thing for example, if you have a patient, this might not be for a Phase I trial but, if you're testing out something that causes hot flushes in people who are post-menopausal and have hot flushes anyway, um, that's not a serious adverse event but it may be a toxicity. And it's such a common event in that natural phase of their lives that it's not even related to disease, it may be a completely separate physiological process that's ongoing and not related to the drug either. So I think that you need to have some clear thinking around how you accumulate toxicity data in a range of clinical trials. It needs to be developed specifically for what the disease entity stage of the disease and the type of drug that you're studying. So the one size fits all is going to be quite challenging I think yeah. [yeah] **(each situation is unique)**

M: Lastly I'd like to ask you a little bit about your experience as a clinical trials researcher. [mmm hmm] In which cancers do you specialize?

S17: Currently breast cancer, previously lymphoma. [okay]

M: And you have your Bach, MD, what year did you receive your MD?

S17: 1976

M: And what year did you receive your medical oncology license?

S17: 1982, 82, 82

M: And do you have any other degrees, Masters, PhD any other fellow, clinical trials related education?

S17: Clinical trials

M: What year did you become a clinical trials researcher?

S17: So I joined in 1982 and I've been doing clinical trials ever since. [okay, great] Yes, so that would mean, yes that is 24 years of clinical trials [yeah that's a lot] mmm, hmm. And I've done Phase I, Phase II and Phase III.

M: And so what percentage of your workload would you say is devoted to clinical trials?

S17: Well it depends on how you ask the question. In term of my own patients, very little these days, probably 10%. But I'm in overall charge of all clinical research for the BC Cancer Agency and I'm the acting Medical Oncology. So everybody doing clinical trials is responsibility, is responsible to me for their academic performance and their clinical standards and their clinical research. So a lot of my day-to-day activities is oversight of clinical research, 25%. [okay] So that's not me directly doing it, it's 10% direct and 25% oversight and leadership.

M: And of your direct clinical trials [mmm hmm] what percentage of that is Phase I, Phase II?

S17: Nowadays I do principally Phase II and Phase III because I'm too busy in my leadership position to do Phase I, so I'm doing 0 Phase Is at the present. [mmm hmm] In the past I used to do a very small volume of Phase I patients.

M: What percent is Phase III?

S17: Um, it's probably 50/50 Phase II, Phase III. [okay, so 5% Phase II] yeah, 5% of the time [yeah, sorry, I've just confused myself] that's okay.

M: Can you tell me about any training that you've received specifically with respect to assigning causality?

S17: Um, directive training I don't know that any of us has received much directive training. But we're all collaborators in cooperative groups where we spend a lot of time discussing causality. So through our participation on committees at the National Cancer Institute of Canada and in the case of some other investigators here, NSABP. We are involved in the discussions and the formulation of the reporting systems for a variety of clinical trials activities. We're all very well educated, but it's been learning on the job rather than signing up for a course. [mmm hmm] And also participating as leaders there.

M: What additional education about assigning causality, if any, do you feel needs to be made available to clinicians?

S17: I think it would be extremely helpful to have an educational forum for young new investigators as they begin their careers on staff. Not so much for residents because they're not filling in these forms as residents and I think it would be too much information for them at that point. But as soon as people join a medical oncology academic facility, even a community oncology facility where they are conducting trials I think that could be helpful. And I think best run through cooperative groups like NCIC. And I think if it's funded through a variety of different mechanisms there would be some specific courses for young investigators on causality. Or indeed completion of, of clinical report forms for clinical trials in general. [mmm hmm] Now some of this evolving, like for example, we all have to qualify that we've done certain ethics committee, ethics training in order to be qualified investigators. So there's some on, online tools you can use for education around ethics. And you also have to prove that when you're audited by Health Canada that you have a comprehensive understanding, we've just had a Health Canada audit, understanding all aspects of clinical trials and doing the causality issues. So I would think the most useful tool to be developed wouldn't

be an assessment tool, it would be an educational tool. [mmm hmm] **(feels training and education is more important than trying to incorporate a tool)** And an educational tool that would be an online tool as, would be helpful as well as potentially some educational forum, perhaps once a year at, nationally, I wouldn't hold this regionally, or through universities, they'll never get their act together. But a national approach under the auspices of NCIC or the Canadian Strategy for Cancer Control or CAPCA would be I think a reasonable thing to do. An educational tool I think would be very helpful.

M: What's CAPCA?

S17: Canadian Association of Provincial Cancer Agencies, they are the people who hire all the people doing all the investigations. [okay]

M: I think those are all the questions that I have for you. Do you have any questions for me?

S17: Oh yes, completely unrelated to the survey, I'd like to see, hear what everybody else's response was to that tool that you showed me.

M: Yes, so what we're going to do is we're going to compile all the information [mmm hmm] that we've gathered through these interviews and we'll be providing each of the participants with an executive summary of the results. [mmm hmm] And our goal is to present at the Fall NCIC meeting [okay] and, and, we also hope to write this up as a qualitative study. [mmm hmm] And then of course this will inform whatever tool becomes developed. But ah, a lot of your comments were quite, you know, many people have, have said similar things. Like a lot of people have crossed out this placebo question [laughter] not relevant at all. I definitely agree with you that there are, it's very vague, some of the questions are extremely vague and need to be better defined. [yeah] Um, I think overall most people feel that this is sort of thing that would be helpful if it's not too

cumbersome and not too administratively burdensome and um. It's really varied, um, in terms of what questions people think are, would be useful. You know things, pk values people said we just don't have that information [precisely it's pointless]. So you know, maybe further on down the line [yeah] we might look back

S17: Months later when all that data comes in say wow, that guy's really high level, maybe that's related to whatever happened you know. [yeah] But at the time it's very hard to make that assignment.

M: So, but I think this is very valuable information and I think you know, this, this needs to be heard by regulators or the people that are making these [yeah] these sorts of

S17: Regulators need to hear it, some sponsors of trials need to hear it, the role of the clinical organization ought to be able to provide I think some educational opportunities. And I do not know whether anything is evolving through the national NIH or the National Cancer Institute in the United States because they do have some online educational things. It's something that I think J or R may have at NCIC. So I think it does help to improve the, but honestly a tool of the nature of the one you showed me is just a joke because any clinician who pauses to think at all can do better than that at first pass you know [right]. So, so a tool has to enhance our capability and not be too dumbed down that it's not helpful or contain questions that are not relevant. So I think the delivery tool is quite a challenge to develop, the educational tool I think would be quite.

M: Okay, well that's great, I really appreciate the time.

Subject 18

M: Even the most experienced clinicians find assigning causality challenging. Many groups such as industry sponsors, clinical trial cooperative groups, research ethics boards they all expect prompt and sensible causality

assessments. But I'm sure as you know, assigning causality isn't always that straightforward and if done poorly it can have implications. [yeah] So we're interested in developing a tool to help clinicians more efficiently and reliably assign causality to, during the Phase I oncology clinical trials setting specifically. [yeah] We feel that by better understanding the needs as a clinician we can develop a tool that is more relevant to you. So do you have any questions then before we start? [no] No, okay. So let's say one of your Phase I clinical trial patients experiences an adverse event, [mmm hmm] let's say it's a serious adverse event. Can you just walk me through the thought process you use when you're assigning causality to that serious adverse event.

S18: Um, I think the thing with Phase I most investigators, and I'm no exception, are fairly conservative. So when in doubt, you know, it's kind of a diagnosis of exclusion but if there aren't a lot of confounding factors, it's a low threshold to attribute it as a possible or probable association. And so usually I kind of look at, multiple things, I'll look at temporality, like was there sort of a before and after thing related to administration of the agent, so time sequence or temporal course. I'll look to see whether, you know, if it's something that improved with withdrawal of the agent. So you know, sometimes you can't make that in real time because the event has happened and you've withdrawn it. I try, and that's harder again with the Phase I to see if it's biologically plausible. So if I have an anti-VEGF agent and I get someone with malignant hypertension and even though it's a new agent but that's the mechanism and I know that's the experience in that class [yeah] I kind of will think okay it's plausible that would have happened. Um, and then, I mean those are kind of the, and then you obviously exclude other obvious confounders. So the workup would include excluding you know, you're of differential things that could cause whatever that toxicity would be. And then you basically, the composite of that and decide, I have to admit, it's infrequent that I can say definite unless it's a scenario where there's really nothing before and the person is well from that systems point of view and there's no confounders and they get the drug and it happens right after you know. So a definite would be like

an infusional reaction and you know that that's happened. But more common it falls in the possible or probable. I don't think I've ever, to be quite honest, had a serious adverse event and been able to say absolutely not, like there was no association in, in a Phase I. That's not true for other things where you have more experience with the agent. **(the less developed an agent, the more it is attributed)**

M: How do you, how would you differentiate between possible and probable, like what, what?

S18: Just index of suspicion so, um, I don't know, nothing fancy. I think for me probably of all of those the biggest thing is the time sequence, like the temporality of it. I don't have a you know, if it meets one of my three criteria I say possible and 2 of the 3 I say probable, it's more of a gut feel. [ah ha, okay] **(intuition)**

M: What are the resources you refer to when you're assigning causality?

S18: Resources, so I will, so if someone has had a serious adverse event, you grade the severity and usually we use the NCIC CTC criteria so. And typically we don't usually that vigorously assign causality unless it's 3 or 4. And then I'll look at the investigators brochure or the protocol to see if this was like a described or known effect. **(more serious toxicities are assigned more carefully)**

M: What do you mean when you say don't vigorously assign causality [well usually] unless it's a 3 or 4?

S18: Well those are the scenarios where you have to do it right away, because if it's a serious adverse event, it's not that you don't do it after the fact, you have time. If it's a grade 1 or 2 you have time to follow it and then see what happened with it, like if you withdraw the agent and it worked. But usually with a serious

adverse event we often have to report it within 24 hours and we have to give some idea of what happened. And often you're asked to give an attribution of what we think is the likelihood of it being related to the drug and make a decision if the patient is staying on or coming off, those kinds of things so. [yeah] It's, so the grade 3/4's are more pressing ones is what I [right] should say. Um, but the resource basically it's looking at the, trying to grade the severity of the toxicity and then looking to see what information you have on that agent you know. So if it's an agent that has, whether it's a lit review or the other Phase Is that are available for it [okay] yeah, that's about it.

M: Where would you get the other Phase I data information from?

S18: Usually do um, abstract searches, Pub Med, often, because they're not really, by the time they're published, you're onto a Phase III. [yeah, so abstract searches] So abstract searches or speak to colleagues or other investigators who have studied the drug.

M: And usually your other colleagues are here or elsewhere [wherever] wherever, yeah, okay.

S18: There's a fairly small community in Canada for people like you know, so if it's a Phase I being done at multiple sites so let's say it's being done through PMH and we're doing it here then we would contact you know PMH. Or if it's being done through NCIC we'd contact the NCIC office and see if this has been reported. [right, okay, good]

M: Are there any tools that you use when you're assigning causality?

S18: Are there tools out there? [laughter] no I don't. **(demonstrates the seriousness of this issue)** [okay] No, other than the attribution scale that just sort of, that tells you how to rank it, it doesn't. I mean there's, like there's those

five, those principals of association versus causality and that's what you follow and I already talked about that. Time sequence, dose response, withdraw it and it goes away [how did you learn about those?] biologic possibility. [you know, do you] I think we all learn it at some point, I don't know where but, it came up at some point in my training I'm sure [in med school or something] yeah, yeah. [what did you call them, principals of?] Well there's a, I don't know what the, if you asked me for a reference I couldn't. But there are sort of 4 or 5 criteria that you use when you sort of say there's something a potential association versus assigning actual causality to it. And the more criteria is satisfied the more you can assign causality to it. And it's usually related to like exposure, risk of expose and an outcome. [mmm hmm] So you know, smoking causes lung cancer [yeah] [so like the Bradford Hills criteria] I don't know the name [yeah, yeah]. But the idea is supposed to be you know, so then they, the example is smoking again, if you, it's biologically possible if you, usually the smoking happens before the lung cancer. If you stop smoking you decrease your risk of lung cancer [mmm hmm] and there's a dose the, the more you smoke the more likelihood you have of getting lung cancer [right, a dose-response yeah] and there might be another one but I can't. But those are the, I think that's the context in which it was initially presented to me somewhere [yeah] but I use it for that. I mean it's for the same idea and it kind of fits, but a tool would be nice. As far as, it's interesting, as you try to articulate the rationing, the reasoning, you know, I'm like well, that's very hocus-pocus. But that's, there isn't, I'm not aware of a refined clinical tool in the trial setting that helps assign attribution. [okay, good] **(again, reiterates the seriousness of the situation)**

M: What would you say are some of the problems or challenges with assigning causality?

S18: I think, um, the, the challenge is what we were just talking about, it's not ah, it's probably not reproducible, like there's a lot of bias, it's probably and there's sort of intra-investigator variability. **(reiterates what was found in the literature:**

low reproducibility of clinical judgment) You know, where the same event can be attributed differently because a lot of things, it's a subjective assessment. It's not as objective as it should be, I think that's what makes it a challenge. **(feels the process is too subjective)** Um, I think any time with an investigational agent, like I said your antenna are fairly high up and you probably are more likely to ah, to lean on the side of, you don't want to harm a patient or subject to harm to assign causality where it may not have. Like assign a higher level of attribution even if it may not have been. So you know, when in doubt the diagnosis of exclusion is going to be that it's, it's the investigational agent. [yeah] So, and that may be unfair to the agent under development right. [mmm hmm] So it's just your level of, you scrutinize it more, like I said a more conservative approach to when in doubt, better to say it's possibly related than not. Those are, and no tool. [laughter]

M: That's one of the challenges. [one of the challenges] So you think a tool would be useful then?

S18: I think, I mean [what would] I mean something that's standardized, something that, that at least, so there is, like some, potentially less variability in how we assign, um, because I don't think it is standardized. I mean there, I have to admit, there are sometimes when um, I will be reviewing SAEs for other agents. Like if it's a trial and we are asked to decide if we are going to submit it to our REB, that kind of thing. And you look at them and they're so obviously not related or they're so obviously related and then they will often tell you in the little synopsis what the investigator felt. And you're looking and thinking, how, how did you come to that conclusion? Because based on the clinical information provided, it either totally doesn't make sense or, and so you. So clearly people are interpreting it quite differently and so, I think it really isn't, isn't standardized. [phone rings] And it's taken for granted that people know how to do it. Do you mind if I get that? [sure]. **(major inconsistencies due to lack of standardization)**

M: So with this tool then, what do you think, what sort of criteria should it, what should it um, look like?

S18: I think ideally, I would think of it like, you know a set of criteria, like 6 or 8 or 10, points and then you could say that if you had, let's say it's a 10 point scale, if you decided there were 10 criteria, if you have 8 or more is definite and 5 to 7 it's probable and 3 to 5 it's possible. Like that kind of a [yeah] something objective, a scoring system I think is probably, something that, something that would be helpful. [mmm hmm] And it has to have some measure of flexibility because people may not have all the information available to be able to do it. Like in the scenario where I said if you have to report it right away, although you can go back and change what your attribution was but it has to be a little bit flexible and should be simple and easy to remember [laughter] and that kind of thing. [yeah] So maybe not ten points. [laughter]

M: What are your concerns about how clinicians assign causality right now? You already sort of touched on that briefly.

S18: Um, I think my concern is I don't know how they do it. **(big statement)** And so you know, we have to trust each other's judgments when we kind of determine the safety profile of something or are presenting it to a patient. So I think, it's just I don't, I don't know how they do it. My concern is that people may be too, may be not as rigorous in pursuing whether it's related to the drug or, or, you know I just don't yeah, I don't know what the, there's no accountability for it, we just assign and that's about it. Usually, I mean for industry sponsor I don't know, for industry-sponsored trials the company will also try to look at it and put it into some context. But the company is not a completely unbiased perspective and so you have to kind of decide for yourself. [yeah, okay]

M: What external influences or pressures from third parties have you felt when assigning causality?

S18: I haven't had any. [no?] No.

M: What I'd like to do know is just give you a quick, what this is, this is a tool that was developed by a researcher named Narjano to help clinicians assign causality to adverse events. I'm just wondering if you wouldn't mind reading over the questions and then crossing out any that you don't feel are relevant to the Phase I oncology clinical trial setting. Have you ever seen this or heard of this before?
[no]

S18: The ones that I feel are not necessary? [well just not relevant to the Phase 1 setting] Probably the only one is the placebo question [number 6, yeah]. You don't have a lot of dose going up and down in a Phase I either, number 8, I don't know how, but it does depend on the trial, sometimes there are dose escalations done within a single patient so I suppose that's possible. But this, this, like I said, the flexibility thing it would have to be, for something like this there would have to be an option to say not applicable like [yeah] something like the scale should be 80% of whatever denominator you have left. That kind of a scale versus absolute numbers. Confirmed by any objective evidence [you don't know what that means?] Was adverse event confirmed by any objective evidence? [yeah I think it's a bit vague too] yeah [needs to be better defined]. I think if, yeah, I think it needs to be defined a bit more, like a rash and did you actually see it? or. [I think sort of what yeah, that means] That needs a bit of clarity. Everything else makes sense yeah.

M: Are there any things that you think are more important than others, should be weighted more heavily?.

S18: I think, to me the whole before and after time sequence I would put a lot of weight on that. [so is that 1 and 3] So 2 and 4 [sorry, 2 and 4 yeah] appear after and then I'd probably say did it disappear for 3 would be the next one, 2, 4, 3.

M: Would you be able to just rank these [oh sure yeah] so 10 would be the most important and 1 would be the least important. [1 is least important] Okay, great, thank you very much. Now is there anything here you think is missing [10 is most right right] yeah, 10 is most important.

S18: Anything missing, no I think this about covers it, I think so. [yeah]

M: And do you think something like this would be too cumbersome or?

S18: If there was some way to collapse it, maybe, because as I look at it, 10 is probably too many points. So if it could be fewer, like some of these are overlapping questions, like the does it get better when you stop is overlapping with the was it worse when you had more drug or less? Like these are, these are kind of overlapping questions, 8 and 3, yeah, they're asking the same thing and there might be ways to collapse them into, into one. [mmm hmm, alright, great]

M: Now I just wanted to ask you a little bit about your experience as a clinical trials coordinator. So, in which cancers do you specialize?

S18: GI [GI]

M: And um, you have your MD? [mmm hmm] What year did you receive that?

S18: 96, 10 years [good for you]

M: And ah, your medical oncology license, when did you receive that?

S18: It was 2001.

M: And do you have any other Master's, PhD or?

S18: Public Health.

M: Oh yeah, where did you do that?

S18: I did it at Boston [okay, the Harvard] Harvard program yeah.

M: What year did you complete that?

S18: 2003.

M: How did you like it?

S18: It was good, a good program, it's good for clinicians I think, its geared towards it's not esoteric, I was able to, you can do it in the summers, that's the beauty of it you know, so it's a good program. [good]

M: Any other certifications or qualifications related to clinical trials?

S18: I mean I did a sort of clinical research fellowship after, from 2001 to 2003 in GI and that was, so that included protocol, writing protocols, involvement in trials and that was at Mayo.

M: So what year did you become involved as a researcher?

S18: Here? So officially, like independent [mmm hmm] 2003.

M: And what percentage of your worktime would you say is devoted to clinical trials?

S18: Oh, you mean actually seeing patients on trials or writing trials and doing trials [all related to trials] all of it, 25%. [25%]

M: And then what percentage of that is Phase I, Phase II versus Phase III?

S18: Oh um Phase I, it's probably, I mostly do Phase II so I would probably say 50 Phase I and II and then 50 Phase III.

M: And have you been a local PI ever here? yeah. And can you just tell me about any training you've received, specifically with respect to [background noise] do you mind if I close this [no] this recorder will pick every little sound up. [oh that's okay] So can you tell me about any training that you've received specifically with respect to assigning causality to adverse events. How did you learn how to do it?

S18: Formally, I don't have any recollection of any formal training. Now, we have to, we have to do, other than when we sign up to be investigators through NCIC you have to make sure you've done the ethics for. I mean the ethics for conducting human clinical trials, the online web thing [yeah] but I don't think we have to do anything that relates to GCP, like Good Clinical Practice, assigning attribution formally. I don't think there's anything. So I don't think, there wasn't very much else unless I slept through that class or I missed it, if there was I haven't done any. [no]

M: I think something is actually in the works [yeah] with NCIC for developing some sort of ah, GCP thing.

S18: That would be good because they have a new investigators workshop, that's really about, this is the NCIC, it's not really about some practical

information about how to like conduct clinical trials. [yeah] And I have to admit the, both through my Fellowship and the Harvard Program there are courses on design and conduct of trials and stuff. But most of them focused on like developing a trial and writing up a protocol. There's not much emphasis on the actual execution part of, of the protocol. So I, I, I don't think there has been that formal training.

M: what additional education about assigning causality do you feel should be made available? You know, do you think something like that would be useful?

S18: I don't think it requires a whole course. I think a tool. Practically speaking if you look at the breadth of people who are involved in enrolling patients to clinical trials and are investigators. I don't think everyone needs to take a formal, I think that's why tools are helpful and the questions are fairly intuitive, like when you read it, it does make sense so so I think it just needs to be standardized. If there was something that everyone had to do that related to GCP and include that and it could be a web based type. Make sure you've gone through that, understand what, what it means when you, like even the grades of attribution and what it means when you assign causality. But I'm not sure it needs to be a big course. [no] Yeah. [yeah, okay, great]

M: I think those were all the questions that I have. [excellent] Thanks very much, I really appreciate your time, I know how busy you guys are.

S18: Yeah, it's a good, good effort I think that, that we do need something at the NCIC level. I'm surprised, I'm surprised there aren't, are there tools out there that are in use [not in use] that in the groups, nothing [no]. **(big statement)**

M: This, this is one that's been developed and there have been others that have been developed but it just doesn't seem like, based on the people that I've talked to, nobody is really familiar with it [yeah] don't even know that it exists [yeah]

never mind using it you know. So I think it would be really good if we could try and get something like this, just, especially for young investigators who are just starting out and really aren't sure how to do this. [yeah] I think once you get to a certain level you, you know [yeah] it becomes second nature but.

S18: Because many of us learn from seeing what other people, like you, it's just very off the cuff and I think a tool would be useful. It's a huge hole. I can't believe it. **(big statement)**

M: Well that's encouraging, that's good, great, thanks.

Subject 19

M: I will just give a little background about what it is we're doing. We're interested in knowing how clinicians assign causality to adverse events during Phase I oncology clinical trials. [okay] And, um, so even the most experienced clinicians find assigning causality to adverse events challenging. But some groups such as industry sponsors, clinical trial cooperative groups, research ethics boards, they all expect prompt and sensible causality assessments. [mmm hmm] But sometimes it's not always straightforward [mmm hmm] and if done poorly it can have some large implications. [mmm hmm] So we're interested in developing a tool that can help clinicians efficiently and reliably assign causality during Phase I oncology clinical trials. And we feel that by better understanding the needs of clinicians we can make the tool more relevant to the people using it. So do you have any questions [no] before we start?

S19: No, I completely understand where you're, the issue.

M: Okay, so first I'd like to better understand the reasoning that you're using when assigning causality. So let's say one of your Phase I clinical trial patients experiences a serious adverse event [yeah] can you just walk me through how you think about the situation when you're assigning causality?

S19: Yeah, I guess there are probably, I mean first of all there's not some rigid schematic that I follow and I don't know that there's one that anybody follows. **(believes no one uses a systematic tool)** Um, so there's, as far as I know there's not an existing template for assigning causality. [okay] I think what I do is typically, obviously Phase Is almost by definition are using new agents [mmm hmm] and so I will look at the protocol or information I have about the new agent. Um, to just see what the expected adverse effects are both common and uncommon with that agent. So the first thing is, you know, is it, is this episode or event something that you aren't surprised to see? You know, is it typical of what's been reported with the drug so far? Um, the second part of it I think is, and another part is the temporal relation, you know, to the, to the drug [what do you mean?] in terms of time. So if it wasn't something that was happening before and it's now happening now that they're on the drug. I mean that is something I think figures prominently in terms of attributing causation, particularly with drug infusions. So um, someone gets a drug and they almost immediately have a reaction, I mean that's obvious. But I mean even if it's within a few days or even within perhaps a week, I think that gives you a stronger basis for causation. [okay] And it's harder with things like chronically administered oral medications right, where the onset of an adverse event maybe delayed as the blood levels of the drug you know, gradually equilibrate in the person. Um, and I think the third factor I consider is the patient and their underlying disease process. Because I think where I have the most problem assigning causation is where it's something that you could blame on the cancer or blame on the drug [right] so I think that's where it's most difficult.

M: Can you give me an example.

S19: I think, I mean, the example to me that comes immediately to mind is ah, is DVT or blood clots, right. So those can occur in cancer patients, especially people with metastatic disease who are typically the ones in Phase I trials I mean they just happen you know. But they also can be related to the study drug you

know, and ah, so when someone develops a blood clot when they are on the study drug, would it have happened anyway?, is it related to the drug? That's where I think issues of attribution become very difficult. [right] If it's neutropenia well then it's probably, it's almost certainly due to your study drug unless you know they're getting bone marrow infiltration from the cancer or something like that. So I think attribution of something fairly obvious like that is a lot easier. [yeah] So I guess, I guess you know, if there's a fourth criteria, so it's the, it's the person's cancer situation and I guess the fourth criteria is it's the type of adverse event, right, [yeah] which I didn't count because it's kind of self-evident. You know there are some that are more difficult to attribute and some that are easy, you know, myelosuppression, low blood counts, it's almost always due to study medication. It would be very rare that you would attribute that to something like the disease process unless you're treating, unless the patient has leukemia or something like that. [paused for phone call].

M: Okay, so you were mentioning that sometimes it's important to look at the type of event.

S19: Yes, recapping, basically it's the type of event, clinical event, is it obviously related to the drug?, or obviously related to the cancer?, right. [yeah] And there are some events that I think obviously are, like neutropenia, unless the person has leukemia or something is almost always related to the drug you know, if it's a chemo cytotoxic agent. Where you know, um, a rash, with some of these drugs have a rash, you know, you give them a pill and they're covered in a rash all of a sudden, you know, those are obviously related to the drug. And there are some things that are obviously related to the cancer, like pain. You know, sometimes I see pain listed as an adverse event and you know, drugs rarely cause pain, they can do it, but usually that's a sign that the cancer is progressing or something right. **(believes pain is attributed to the disease not the agent under investigation)** And then there's the timing, so there's the, you know, if it's obviously, you were well one minute and then you took the drug and this

happened it's pretty hard to argue that there's not some causality there. [right] Although occasionally that can be coincidence, but most of the time the temporal relationship in terms of time quite useful. But there do remain some things like fatigue, blood clots, nausea, you know these types of things that are not always easy to clearly attribute to the ah, to the drug or to distinguish from the underlying disease process, right. [yeah] Um, sometimes it's really helpful to really carefully evaluate those symptoms at baseline right. So what is the level of, and we don't always do that, so what is the level of nausea or fatigue at baseline? And often when you look back you find, yeah the patient did have some nausea even before they started the drug right. You know, they're on narcotics or something that was causing nausea. Whereas if they had nothing like that, then I think it makes the attribute, attribution of those types of you know, sort of experiential symptoms of the patients easier to attribute to the drug. [yeah] Where you know, so I guess that's sort of how I do it. [okay]

M: And what resources do you refer to when you're assigning causality? You mentioned you check the protocol.

S19: Well typically you will have information about the drug itself or drugs under study in some form. It maybe the study protocol, or some, it maybe the investigator's brochure, um, I mean sometimes you might have to go to other resources like the CPS or go on the Internet .You may sometimes have to call up the principal investigator you know, um, I've haven't, I mean I probably have done that but that's rare. Um, so there's and, and pharmacists as well [yeah] you know, if it's an experimental drug they may sort of know as little about it as you do you know. [yeah] But if you're giving drug combinations for instance, that contain more standard agents that can sometimes be helpful to rule out attribution to the other agents and be able to attribute it to the investigational agent. **(have to get information on the protocol drug from a variety of sources, a lot of work)**

M: So if you were doing a study when there's a combined therapy.

S19: Yeah, most of the Phase I studies I've been involved with, because we don't do first in humans very often here at our centre. [mmm hmm] When I've done a Phase I it's typically been ah, adding a new drug, molecular agent onto a standard chemo drug. [regimen yeah] You know that type of Phase I. [okay, good]

M: And, um, what tools then do you use when assigning causality, are there any sort of tools that you are aware of or that you use, any kind of?

S19: Tools, well you know, I'm always asking my CRA's um, what, I mean, I don't know what they're called, but there's these quality of attribution scales. [okay] Like, and I don't like these are the things like definitely related, probably related, um, you know, possibly related [yeah, yeah], unlikely to be related, unrelated, those types of scales. I'm not sure if those are standardized, my perception is that there's some variability in those scales. **(suggesting standardized measuring criteria)** And in some trials almost a yes or no [yeah] you know, is it related or not? and you know if there is any uncertainty that makes attribute, I think that brings a lot of potential for misattribution in. But also, to miss, when I say mis- attribution I mean, attributing it wrongly to the drug or not attributing, missing attribution as well as mis-attribution. Um, some had a DVT for instance that could be related to the drug and if you had to say yes or no, oh this person had cancer, this is related to their cancer, it's not related to the drug. But that might be an important attribution that we miss. So when you don't have a, when you're forced to yes or no it um, I think that can bring in a lot variability in attribution. **(sometimes feels forced to make a decision when they are genuinely uncertain)**

M: So you prefer the scale?

S19: I think a scale is much better but I think there is also variability in the scales too. I'm not sure if there is a standardized attribution scale or not. You know, we have standardized toxicity scales in terms of grades for toxicity [for grading] yeah, and those are quite useful. But then when you want to attribute the toxicity you don't know exactly what you're going to get and you have to sort of look and use whatever is on the CRF right. [yes, okay] So it would be nice if there was a standardized attribution scale. I personally like the ones that have a number of gradations of attribution, um, you know, likely, probably, possibly, definitely, you know that's my own preference. Because it still allows you to be black and white about it if you're sure it's the drug, it's definitely related or it's unrelated. But also there's you know, for some of those other types of events I talked about, mentioned earlier it allows you to kind of grades of attribution where you're not quite sure. [yeah, yeah, okay, great] **(takes comfort in having the flexibility of scale attributions)**

M: What I would like to do know and just ask you to consider a scenario for me. So let's say you're treating a 65-year-old female breast cancer patient with a confirmed diagnosis, sorry patient with a confirmed diagnosis, she actually has metastatic breast cancer. [okay, yeah] And she is in a Phase I trial [mmm hmm] with a new investigational drug and she experiences a pulmonary embolism. [okay] Sound familiar? [yeah, I called it] How would you assign causality to the study drug if there was a 75% chance that the adverse event was due to the study drug and a 25% chance it was due to other factors. So lets say adjuvant treatment, disease progression.

S19: Well that's a typical dilemma isn't it? [yeah] I would in that case say probably but not definitely. [okay] Because metastatic breast cancer patients do get blood clots and they do get PEs. But where, how I translate that information is this drug is associated with thrombosis because you're saying 75% and therefore that is important in terms of the data you collect from this trial that, that event is associated with the drug in some way where you can't be definite. I don't think I

would say it's definitely associated though, I just don't think you could do that um, in that clinical scenario. There is some uncertainty that this patient might have developed, had the PE anyway. [mmm hmm, okay]

M: Now what if those percentages were changed so that there was a 50% chance that the adverse event was due to the study drug and a 50% chance it was due to other factors. [50/50] Yeah and the scale is certain, probable, possible or unlikely.

S19: Certain, probable, possible, unlikely, it's either probable or possible. Again I would because the person is in a trial I would probably say probable if it's a 50/50 toss up. And that would be because my bias for a person on an experimental drug is to report any adverse events that could be related to the drug. And I think if you said possible there, you wouldn't be wrong in accuracy, but it slightly downplays the importance of the severity of this event. You know pulmonary embolism is a severe adverse event and if it's, if it's even possibly related to the drug um, I think that's important to document and publish in the results of the study. So I would say probable. [great]

M: Now what if there was a 20% chance it was due to the adverse event [20%] and an 80% chance it was due to other factors?

S19: Then I'd say possible.

M: Then you'd say possible [yeah] okay, great. Just trying to get a feel of how people are interpreting [yeah] those terms you know. [yeah]

M: Now what would you say are some of the problems or challenges with assigning causality?

S19: Well I think one problem is simply documenting events.

M: Why is that?

S19: I don't think patients always tell you everything that happens to them. Um, then there's **(feels there is a disconnect with the patient)**

M: Why is that do you think?

S19: I think it's human nature to forget things [okay, forget] and obviously if it's a very serious event, it's going to be recorded and you're likely going to hear about it in some way. But not all patients understand that in a clinical trial that we're also interested in the side effects of the treatment. And in a Phase I actually toxicity is your primary endpoint. [mmm hmm] But the patients of course feel that they're on the treatment to help their cancer [yeah] so there's a little bit of a disconnect there. So they're more interested in what the drug is doing for their cancer and they kind of are hunkered down with the idea, many of them are very stoical right [yeah] they say I'm going to put up with whatever side effects I have to put up with um, to get through this treatment because it's going to help my cancer. And I think that's, that translates sometimes to a lack of reporting of events. I think that some patients may also perceive that you know, the doctors or nurses don't want to hear them complaining right, they just feel that they'll sound like whiners right. [right] And now there are some people who are more than happy to talk to you for a long, long time about everything that's bothering them. [yeah] So you know, it's just this sort of spectrum of human nature, it's just how people are. Um, they're, and some people are you know, very obsessive/compulsive in their personalities, they keep diaries and they can show you day-by-day what their side effects were. And other people are not like that at all and they just don't record it and then they forget, there's just that difference in personalities. I think then there's, assuming that the patients report the events, there's the recording of the research people or nursing staff, right [yeah] or the physicians themselves. So there's actual, I mean you just may forget to write

down an event, especially if the patient is having a lot of side effects you know it just may be missed. **(human nature adds bias to the trial)** So I think basically recognizing and recording that this adverse event actually occurred is something that happens you know. So that would be a barrier to you know, attributing it if you don't even know it happened. Um, other barriers to attribution.

M: Just, just problems or challenges yeah.

S19: Well I think you know when you're dealing with a lot of new drugs and doing a lot of drug trials it's hard to keep track of some of the idiosyncratic or unique adverse effects of some of these drugs. So you have to, as I mentioned earlier, knowing the drug and it's potential side effects, um, you know is sort of key in a way to attributing. **(you really need to know the drug well)** And if you're so busy or have not done your homework in terms of reading about the drug, or don't have the time to go look it up. So you know, basically just having a busy clinic and being busy at work can lead you to mis-attribute these things right. **(but time pressure take away from this)** So care has to be taken you know, in terms of both the identification recording and attribution. Um, I guess another potential barrier is sometimes when you're dealing with Phase I drug trials, new side effects occur that haven't happened before right. And you just may not think it's due to the drug, you know, you look in your documents and that's never been reported [mmm hmm] and um, I mean you have to realize something like a blood clot would be typical because um, typically in a Phase I trial the drug has not yet been studied enough in humans to know if it increases the risk of thrombosis right. [yeah] Which may happen in 5% of people treated, but if only 50 people have ever got the drug before, none of them may have actually experienced that. And then when you see it in a patient, ah, you know, you'll look at your information and say well this has never been reported with this drug, this drug doesn't cause clots. But in fact it does and it's just an issue of you know, a very infrequent but serious event [yeah] that, that's you're seeing the first event of it. And that's always with Phase I trials, that's always the thing I worry about when I

see something strange, is this, you know this hasn't been reported with this drug before, but is it due to the drug? And ah, um, and so I think that can lead to mis-attribution as well you know [right] people will think, oh doesn't cause clots and it's definitely not related to the drug when in fact it is. [yeah] And as time passes and more people see it then the idea of attri, the awareness of that attribution becomes you know, ah, prominent. But, but you know when you see it the first few times people may just wave it off [yeah]. What else, so it's about what impedes attribution was your questions right?

M: Well just any problems or challenges [Challenges, challenges] that you encounter when trying to assign causality.

S19: Yeah so [that's pretty good] I've covered all the bases there. Patients don't report it, doctor's don't record it and doctor's don't know what, know of it, either because they haven't read it, or are not familiar with the drug or it hasn't occurred before. I think those are the main things. Um, I think um, other drugs can confuse the issue too, make attribution difficult.

M: Other study meds? [just other medications] yeah any other meds.

S19: And other medications yeah, concomitant medications, I think that's it, that's everything.

M: What are your concerns with how clinicians currently assign causality?

S19: Um, well I think, I think there is some variability in that. I think clinicians may, and that is due to a number of factors, I've mentioned some already but I think some physicians whether it's business or lack of care don't know enough about the new drugs that they're giving to people to appropriately assign causality. They don't have a clear cut attribution scale, I think there may be differences in what one person thinks is probable and another person thinks is

probable, you know what I mean? [mmm hmm] We don't get any education about this right so as a part of GCP training we are taught about serious adverse events and yada, yada, yada, but no one ever goes over the difference between definitely, probably and possibly, you know. And ah, I mean I think I know what it is, but that maybe very different than my colleague next door [that's right]. So I mean we're assuming everyone is using the same definition of those terms but I'm not so sure. I mean I think you already illustrated with the earlier questions where my sort of cutoff is between possibly and probably but that may be different for somebody else right. [right] So if you only consider events probably or definitely related, that difference between physicians and those labels could be important right. [yeah] Um, yeah I think um, I think those are the main things I'd mention there. [okay, great] **(lack of consistency with grading scales, leads to inconsistencies in attributions)**

M: What external influences or pressures from third parties have you felt when assigning causality?

S19: Third parties, um, our CRA's sometimes want things attributed in a certain way.

M: Really? [yeah] how, how attributed in what way?

S19: Well, they'll often, I think they often do a lot of the causality assignments, sorry the attribution type of assignments [phone rings]

M: Okay, so you were saying that um, the CRAs tend to attribute causality.

S19: Yeah, I was just thinking they're, when you look at attribution of adverse events, I mean they're basically the people you're working with [yeah and they want] you think you're filling out a CRF and then um [they] they want an attribution level. And ah, sometimes they have their opinions about what the

attribution is and they're different from [yours] mine. You know, not a lot but um, that just in terms of explaining to them and then they have to change their forms [yeah, yeah] and if they've already submitted the forms a certain way. Ah, in affect you're creating more work for them, ah, so that does, I don't like to create more work for the people I work with. So I do feel a little bit of pressure there, but ah **(feels pressured to conform to certain causality attributions in order to create less work for others)**

M: Now is it usually that they want you to attribute it a little more one way than another way?

S19: No, no, it's usually that they've made an attribution and because it was say serious they had to submit a CRF immediately and for whatever reason they had to do that, maybe I wasn't around [yeah]. It just had to be done and they and then when we go over the event my opinion of the attribution is actually different so then we have to revise their paper work right. [right] So you know, there's a small bit of, do I really feel this is important enough or strongly about this distinction that it's worth putting this person I work with through revising their paperwork right. [right] You know, this doesn't happen often, but that would be, if I think about it off the top of my head that's the only time I've felt pressure about attribution. [yeah] Um, um, but that's, but that's not a pressure where I feel I'm being under duress to, to ah, mis-attribute something if I think it's the right, the wrong thing I will change it. [yeah] Because ultimately as the PI I'm responsible for all the, what's in the CRFs. And they do their best and usually they're right, but these are very infrequent disagreements. [yeah, okay]

M: Any other pressure [no] influences from third parties?

S19: No, no that's it.

M: So from your perspective what would make assigning causality easier?

S19: Um, well I think some type of very accessible documentation about the adverse events of the medication. I often actually look at the letter of information that was given to the patients [the consent form] the consent form yeah. Because it's there, it's summarized in a fairly succinct way and often it's put into common, less common and rare [yeah]. And ah, as a physician I really don't get that from a protocol. In a protocol, the toxicity, you're reading from off of several pages of material, so just what do we know?, what are the bad things that we know this drug does, commonly, uncommonly and rarely? That would be nice, because as I say the first part of this is distinguishing is this due to the drug or is this due to the disease? And the second part would be a commonly, a universal scale of attribution that once you learn it, you know it and you have some comfort that all physicians are using it in a similar way. [yeah] Just like we use grading for the NCI toxicity scale, you know what a grade 3 neutropenia is. Um, so, you know, basically common definitions and gradations of attribution I think would be useful. [okay]

M: Anything else?

S19: Um, well I guess the only other thing would be good recording and reporting of adverse events. Um, we use a PAR form here, which is sort of four pages of questions listed, you know, the gradation of toxicity across the top and the types of toxicity along the side. And just circles and comments about the duration and I find that very useful. I don't think that's in use at all centers [no] but in terms of recording so you know it cues the person doing the forms whether it's the nurse, the CRA or the doctor to ask these questions. So it's less likely a patient, and it's fairly comprehensive and it asks at the end anything else basically that we haven't asked you know, so open-ended. [mmm hmm] And ah, it would be hard for me to imagine that you know, unless a patient was making a concerted effort to not tell you about something, that you wouldn't pick up an adverse event using this tool. And you have the toxicity right there and theoretically as well you have

the timing. So with that piece of paper um, it helps me a lot in terms of attribution you know, just having an accurate and useful record of the timing, severity and type of adverse event and all of the adverse events recorded. So, I think um, obviously recording and documentation is critical. [very good] It's harder when people get hospitalized and you know with a, you know, away from, out of town, hospitalized in Stratford with some event and that often creates a nightmare of, of ah, recording side effects and timing and severity and whether or not they're due to the drug.

M: And why is that, is that just because it's difficult to get the records?

S19: It's, it's the documentation aspect. When you're doing it retrospectively right, the patient has been admitted somewhere else, they come in and see you days later or a week later and you're just trying to go through it all, to get the timing down, the severity and going from written medical records. It just, it doesn't happen often but it's a lot of work when it does happen so it's to be avoided. [yes, laughter] **(maybe due to time pressures)**

M: What do you think is essential then for a causality assessment tool? What are some of the most important things you know, in order for you to use it?

S19: Causality assessment tool. Well I think a couple of them we've already touched upon, one is it has to have gradations of causality because it's clear there's a grey area, often a big grey area for some of these types of events. **(deals with uncertainty by scaling)** So it has to be gradation, it's can't just be yes or no, black or white, a dichotomous type of instrument. Um, it's um, it's um, it's got to use definitions of causality in terms of the level of causality if you will um, that are understandable and for which there is pretty universal agreement. Or where you could even put in the definition of what it means, probable means, you know, that there is at least if you know if you do this questionnaire on 100 physicians and they all say at 50% I still call it probable but any less it's possible.

Then you could write in probable means that there's at least a 50% chance this problem occurred due to study drug right. [right] So theoretically you could quantitatively define probable, each of these definitions, that would be nice. Um, and ah, and what else? Gradation ..., and that you know it's used all the time right, so that from study-to-study, drug-to-drug you're not using a different scale, you know a different causality assessment instrument or tool. [yeah] Um, those would be the main things. [great]

M: What I'd like to do now is just a quick exercise. If I could just ask you to read over these questions [mmm hmm] and cross out any that you do not feel are relevant to the Phase I oncology clinical trial setting.

S19: Not relevant to assessing causality to Phase I oncology clinical trials. Yeah, I think they're all relevant.

M: Okay, now would you be willing to just grade them from most important to least important? So most important would be 10 and least important would be 1. [okay] Yeah, just rank them in order of importance.

S19: Rank in order of importance in assessing causality. This is hard, it may take me some time here, you may want to go for coffee and come back in 10 minutes.

M: It's just a general guide, you know, there's no right or wrong answers. [okay that's my gestalt] So least important was whether there were any alternative causes that on their own could have caused the reaction. [right] Why did you rank that as least important?

S19: Um, because I think I always assume the reaction, if someone is on a clinical trial I assume the event is related until proven otherwise. [okay] So the fact that there might, you know if someone has a massive PE, the fact that they've got cancer I consider that a possible cause. But until, but I assume that

it's due to the drug until proven otherwise, you know for a serious type of adverse event. [okay]

M: And most important was did the reaction reappear when a placebo was given.

S19: Yeah, we almost never, never do that, but ideally that is what you do either re- challenge either with a drug or with a placebo. So we do re-challenge people with drugs and I think some of the other comments there were you know, re-appears with re-administration. But we don't actually re-challenge people with placebos, I've never done that. [right] But if someone had an event and it re-appeared with a placebo that would rule out I think that it was due to the study drug right. But we don't do that experimental design. So optimally you might want to do that with some reactions, like nausea for instance or fatigue or things like that. Those one's in the grey area, in a way, if you could give n of 1 placebos infusions. But you're talking about Phase 1 trials here which are usually uncontrolled right [yeah] you don't have a comparison arm where you can, so um, in those type of trials you, I've never have one where you'd give a placebo infusion to rule out attribution to study drug, but it's a good idea. [okay, great]

M: Um any other, did you have any other thoughts as you were going through this?

S19: Well I think the idea of re-challenging you know, um when I have to attribute something it's usually at the time okay. [yeah] And so I think an important point that came up after reading that, was yes attribution, you should be able to revise it with time. So typically after the first cycle of a drug um, you're asked for an attribution if someone has an adverse event. But as you go on with the treatment and you modify the dose and re-challenge the patient with the drug, that may give you more information over time. You know, as it says in here, by increasing the dose, decreasing the dose or even just re-administering the dose. That gives you more information about attribution right. So someone got a rash, you

thought, ah that's nothing, and then you said it's unlikely to be study drug. And then you re-administer it the second time around and they get the same rash and it's a little bit worse well suddenly now it's not possibly or probably related right. [yeah] Where at the first cycle you weren't sure and you were and because it was a minor sort of thing, tending to probably under-attribute it right. So I think from reading that, that's

M: It's important to be able to revise your causality. [yeah, right]

S19: But we don't actually, I don't think we actually do that very often, right it's causality at that time, at that cycle, at that point-in-time, right then, right [yeah]. As opposed to, over the course or treatment did it change the causality? Now sometimes I do, I have been asked to revise causalities in that way, retrospectively, okay, retrospectively reassessing causality [by who? by the sponsor?] typically by, presumably the monitors right. [okay yeah] You know, monitors ask the CRA's and then I look over the chart and the history and I go oh yeah, I guess I wasn't sure about that the first time but now it seems to be related right. [right] So yeah, so the repeated treatments, I think you're right, can give some, a lot of insight into attribution. [okay, great] **(may be a result of time constraints)**

M: Were there any questions that you felt weren't on here that should be included, anything that's important but not there?

S19: Ah, I don't think so, I mean I think, pre-clinical evidence is covered, previous conclusive reports, that can be in animals or humans, confirmed by objective evidence. So pre-clinical aspect, you know, if it causes it in monkeys and dogs and rats and you see it in humans then you know, you are probably going to attribute it to the drug right. [yeah] So I think that covers those points. Um, yeah, that's about it. [okay, good]

M: The last thing I want to ask about then is education around assigning causality and you did mention this briefly. [mmm hmm] Can you tell me about any training you've received specifically with respect to assigning causality to adverse events.

S19: Just the school of hard knocks [laughter] just doing clinical trials. I haven't received any specific training about that. [okay]

M: What additional education about assigning or attributing causality do you feel should be made available to clinicians?

S19: Um, well I think some of those points that you raised up there in those questions were good ones, did it, you know, changing drug dose, did it get worse, did it get better you know with repeat infusions, by stopping the infusion, those types of observations. Some people are pretty scientifically minded and others are not right. You know, they're just not in that frame, I can't assume that all clinicians have the same level of um, observational skills with their patients, you know what I mean. **(mind frame, individual variation)** [mmm hmm] In terms of how closely they observe what's going on. So I think that just, if it's really a scientific experiment, you know, when you're giving a Phase I drug to a patient you know, I don't know that all clinicians have that, have been trained with those sets of observational skills [right] right. Um so I think emphasizing, you know just going, those points of what to look for, don't assume anything, record it, thorough documentation. **(feels a stronger level of observational skills needs to be achieved)** Um, and then you know, issues about the definitions of attribution you know, what does probable mean?, what does possible mean?, what does unlikely mean? [yeah] that type of thing. [okay great]

M: Well that's all the questions I have for you. I was just wondering though does, is there anyone else that you recommend I speak to while I'm here?

S19: Um, you've got V. You should probably talk to MM.

M: Is she a Phase I investigator? [yeah]

S19: She's actually trained in Hamilton and she sort of wants to get involved more. She's our drug development person, she's new.

M: So she's a clinician, she's actually a medical oncologist.

S19: She's a medical oncologist yeah [okay, great] definitely talk to her. So V, me, M um, you're talking to T [yeah]. You could um, W next door has done a lot of trials during his career, he's an older guy, I mean I don't know, I mean if you're looking for more rather than less you could interview him. [great] Anybody else um,

M: That's good, we're just looking at, I know you guys don't do a lot Phase I trials here [yeah] anyway.

S19: It's pushing it if it's about Phase I really [yeah]

M: Perfect, that's great.

Subject 20

M: I will just give a little background about what it is that we're doing. I'm working with Dr. A at the Juravinski Centre, you know him [right]. We're interested assigning causality to, how clinicians assign causality to adverse events that occur in patients during Phase I oncology clinical trials. [I or Phase I and II] Yeah, Phase I, Phase I/II.

S20: Because I don't have any experience in Phase I.

M: No, so early oncology clinical trials [okay] when very little is known about the drugs [yeah] just sort of finding, looking into the toxicity of the drug more or less.

But as you know even the most experienced clinicians find assigning causality challenging and many groups such as industry sponsors, clinical trial cooperative groups, research ethics boards, they all expect prompt and sensible causality assessments. And that's not always straightforward and if done poorly can have large implications. So we're interested in developing a tool to help clinicians efficiently and reliably assign causality to adverse events during Phase I oncology clinical trials. And we feel that by better understanding your needs as a clinician we can make the tool more relevant to you. [okay] So do you have any questions [no] about what we're trying to do? Okay, so first I'd like to better understand of the clinical reasoning that you use when assigning causality. So let's say one of your Phase I clinical trial patients reports experiencing a serious adverse event, or Phase I, Phase II clinical trial patients experiences, reports experiencing an adverse event. Can you just walk me through how that situation, you know, the reasoning you use when you're assigning causality to that SAE?

S20: Well I think what you've got to look at is the relationship to the administration of the medication. For instance, if it is an event that the patient has a symptom that they never had before so it can't be easily related to any previous disease the patient's had. Ah, or if um, this is something that is, is, um happens shortly after the medication has been administered I would be more concerned that this might be related. **(temporal association)**

M: What do you mean when you say shortly, how shortly?

S20: Well that's a good question, if it's during the administration of the drug then obviously there's a potential possibility that it could, I mean I say at least possible that it could be related to the study medication. [yeah] If it's after the drug administration, um, again this is probably something that's a little bit difficult, it would be, I guess, what could we say, if we knew in animal studies that there were certain side effects and we saw similar side effects in people, obviously there's more likelihood that there would be at least a possible causality. [okay]

Um, if there were side effects in animal models and say animals had some transient um, myocardial changes for instance[okay] or say pathology and the patient say has a, say for argument sake, the patient didn't have any history of angina, but say he had high cholesterol and hypertension and developed um, some arrhythmias I would say it's possible this could be related to the medication at least [based on what was seen in the animal study] based on what was seen in the animal study. **(baseline is important)** So I think you would have to infer a little bit from the animal data. If the patient say has had a previous history of arrhythmias and develops an arrhythmia, I think it's going to be difficult. I think if it occurred during the administration of the study drug you couldn't rule it out. If it's something that occurred a couple of weeks later ah, it would depend possibly on what are the pharmacokinetics of the study drug, what's the half-life of the study medication. [okay] I think that's all.

M: So you look at the timing, the relationship to the administration and you also look at whether it's been seen before in animal studies. [right]

S19: The other question might be does the severity of the side effect, would that play a role? You know if somebody had a sudden death that was unexpected that would be a concern and you would have to say it's a possibility. Um, if there's a serious event, the patient developed pneumonia you would have to look at some of the extraneous factors. Maybe there was a virus going around in the community and the patient has a previous history of bronchitis. In that type of situation, especially if the drug didn't have a side effect such as neutropenia or any impact on the immune system, you might say well less likely this is related to the study drug and you would probably say unlikely. So severity doesn't necessarily mean it's related to the study medication, but obviously that would have to be looked at very carefully. Um, if the, I think I mentioned this, I think if there is any absolutely new symptoms, the patient has never had any before [yeah] that would be and if it's persisting in particular, that would make me suspicious. [okay]

M: What do you mean when you say persisting, persisting for how long?

S20: Well you could have say somebody who has transient heartburn, that might be one thing but if somebody has persistent heartburn lasting for a week or so after the medication and especially if they required some sort of intervention, that would be [yeah], that would be fairly significant and you would have to say it's possible. [okay, alright, great]

M: What are the resources you refer to when you're assigning causality?

S20: The most important one is the patient, the history. **(Feels knowledge of the patient is more useful than information on the agent)**

M: Sort of what they tell you, their oral history?

S20: Absolutely and we get that by um, ah, the patient has a, has a, self-questionnaire that they fill out, a patient assessment review form [mmm hmm] called a PAR form. And we, I will then actually focus in as well and ask the patients in more detail about those symptoms. Um, also I would normally, again, just to make sure things are covered, ask the patient are there any other, other things, even if they may have answered negatively just in case there is something not fitting on the PAR form that they may have noticed. Besides the patient, family members, maybe differences in behaviour, maybe some psychologic or neurologic issues associated with the medication because we just don't know enough about them, ah lab work, imaging results sometimes [okay] and the physical examination.

M: Okay, any other resources when you're assigning causality when you are thinking about whether the event is attributable to the drug?

S20: Um, well I've talked about how I might, think this might be causal, I think I pointed out most of the information sources I would use, I think those are.

M: Okay, that's, there are no wrong answer here. What tools do you use when you are assigning causality, I mean, you talked about resources?

S20: Sorry the other thing I didn't mention is the other source of information would be the nurses in the chemo suite administering the chemo also. [okay, good]

M: And what about any tools, are there any sort of tools that you use when you're assigning causality?

S20: I'm not sure I know what you mean by tools. **(not well known even amongst experienced professionals working in the field)**

M: Okay, say like a flow chart or an algorithm or a decision tree.

S20: No, no.

M: No, are you aware of any?

S20: No. I think we basically use our medical judgment and the sources of information. [okay]

M: What I would like to do now is just ask you to consider a scenario for me. [sure] So let's say you're treating a 65-year-old female patient with a confirmed diagnosis of metastatic breast cancer. [okay] And she is in a Phase I/II trial with an new investigational drug and she experiences a pulmonary embolism. I am sure this is probably a pretty typical scenario for you. [mmm hmm] How would you assign causality to the study drug if you knew that there was a 75% chance

that the adverse event, the pulmonary embolism was due to the study drug and a 25% chance it was due to other factors, such as disease progression, other study medication ...

S20: I would have to related, it would have to be causal.

M: Okay, so the scale is certain, probable, possible or unlikely.

S20: Probable.

M: You would say probable, okay and why is that, you seem pretty certain about that.

S20: I think just because, although pulmonary emboli are associated with metastatic disease in particular we know that administration of drugs can also increase the risk of pulmonary embolism. I think you have to err on the side of caution when you're ascribing, particularly a potentially serious event to a study medication. Um, I think, and the other, the other thing is that some study medications maybe associated with various line placements that maybe implicated. And I guess we have to look at the

M: Line placements, what do you mean?

S20: that's a PIC line placement may result in a thrombus for instance, going quite, say involving the subclavian vein occasionally, especially with Phase I drugs that's not that uncommon. Um, I realize that things like pulmonary embolism may not be related to the study medication but that, that just has to be compared with other Phase II data realizing that some of this is part of the underlying baseline noise that patients with metastatic disease as well. But you have to, I think you have to assume that you don't know enough about the drug that it could be drug related. [yeah, okay good]

M: Now what if there was a 50% chance that it was due to the study drug and a 50% chance it was due to other factors.

S20: You still have to relate that it's probable.

M: Given that same scale, certain, probable, possible or unlikely. You'd still say probable.

S20: It's either possible or probable. I would say probable. [okay]

M: And what if there was a 20% chance that it was due to the adverse event and an 80% chance it was due to other factors would that change anything?

S20: Well then you're getting into, I guess the first question I would ask is how do you know when you're doing a Phase I trial that it's a 20% probability?

M: I know, it's a very hypothetical question, it's really not realistic at all, but I guess we're just trying to get a sense [yeah] of how you understand those terms.

S20: Yeah, so then I mean obviously it's less than 50% so it's not probable but it's possible [okay] if you're looking 50% as the cutoff.

M: And that would sort of be your cut off?

S20: Yeah. It would make sense to me.

M: What would you say are some of the problems or challenges with assigning causality?

S20: I think a lot of it sometimes is the background noise from patient or the disease. And how do you know the symptoms are not related to the cancer or to

underlying symptoms from other comorbidities from other chronic diseases the patient may have?

M: Is there anything you sort of use as a general rule to help you sort that out?

S20: Well sometimes it's difficult, somebody, say somebody with chest pain who has plural metastasis it's really hard sometimes to know whether this is related to pulmonary embolism. Then basically have to do the appropriate diagnostic imaging which in that case would probably be a spiral CT scan to try and sort some of that out. Um, what other symptoms? say patient fatigue, ah, well that can be really difficult for instance, it could be related to disease, study drug, could be related to psychologic factors, some change in the patient's environment, who knows? And that could be, and you have to look at all those and figure out which is most likely and then it's you know, and have there been changes in those areas that might explain it? Um, and if there's more than a couple of possibilities you have to kind of use your judgment which is more likely. [yeah] **(process of elimination)**

M: Okay, any other problems or challenges when it comes to assigning causality?

S20: Um, yeah if you were looking at, at, lab testing, is um, worsening anemia is it related to the study medication or is it related to bone marrow infiltration by tumor? Um, that could be extremely difficult to sort out and I think what we have to do then is okay, let's look at what was happening maybe before the patient got on the study medication. Was there worsening ah, bone marrow functioning beforehand and if this is just a continuation of what was happening beforehand, probably more likely related to the disease than to the study medication. If this is something that's relatively new, um, then you've got to look at the disease process and find out whether there's been some recent new progression of disease in the bone that would corroborate this as probably disease related or if

there isn't then I may be a bit more suspicious that it's medication related. Other things that could interfere that you have to check out as well, for instance, nutritional causes of marrow function, the patient may be becoming folate deficient, vitamin deficient in some way, maybe having some blood loss for another reason. So you have to kind of look at everything. [yeah, okay]

M: What are your concerns about how clinicians currently assign causality?

S20: [laughter] I guess, I guess one of the biggest challenges these days is that if we, people have enough time to rigorously evaluate all the possibilities in a very busy clinic setting. [yeah so] The time to sit down and really fully go over everything with the patient in terms of what's new by history and do a good physical examination. **(see time as the most significant constraining factor on causality assessment)**

M: So you're concerned that might not be being done right now?

S20: Um, I think everybody's under severe time pressures these days and it makes it, it's um, you need to have a dedicated infrastructure to do good Phase I and II studies.

M: So what's involved in that, infrastructure, what do you mean?

S20: Um, I think you need good clinical trials nurses, good experienced clinical trials nurses. Um I think you need to have appropriate time in the clinic to assess the patient. Ideally you should, we should have things like clinical trials fellows to facilitate in the research. Um, I think ideally what would be really nice is to have a clinical trials kind of organization, Phase I or II organization where people could meet regularly to, so that they are aware of some of the issues to keep the quality assurance of the clinical trials as high as possible.

M: Hmm, that's an interesting idea.

S20: It's a bit of thinking out of the box [good for you, okay].

M: What external influences or pressures from third parties have you felt when assigning causality?

S20: None [no] I've never felt any. [no, okay]

M: And from your perspective what would make assigning causality easier? [Ha, ah] Other than the obvious, having more time.

S20: That's an interesting question. I'm not sure if there's any shortcuts to this. Um, maybe others have thought about it a bit more than I have but I, I think you need to um, you need to have a good history from the patient each time. You need to have a good physical examination, and you need to have experienced people involved in the clinical trials. Um the more you have of that, the more you have some protected time to do that, the more accurate the information you're going to get. Um, I, I, the um, there are too many, especially now that they are moving into molecular treatments and biological treatments and when we start using that in combination with other agents there are too many unknowns. And especially, I mean, the data that I've seen not too long ago where we've seen information from animal studies that suggest that combinations of agents seem to be well tolerated. And we moved to the human setting and get a completely different result. I don't, I think it's very difficult to try and make any assumptions.

M: Can you give me an example of something like that?

S20: Well there was a neat, there was a neat presentation at the I believe, San Antonio Breast Cancer meeting in 2004. And I'm trying to remember the name of the fellow, I think it was a guy that used to practice, who used to be at the

University of Toronto and he's now in one of the facilities in Texas. And he presented a neat ah, um, um, antidote about some mouse studies using combinations of biological agents where the mice seemed to be doing pretty well, they had really good results in terms of tumor regressions. And they started doing the Phase I and Phase II trials in humans they had all these unexpected toxicities.

M: You don't remember the name of the drug though eh?

S20: Ah, it was a combination of tyrosine kinase inhibitors and stuff, it was a bit of a cocktail [okay] I don't have it at my fingertips. [no I'm sure there's so many]

M: Yeah, so that's, that's definitely a challenge when you're using these biological targets and they don't perform as expected.

S20: In oncology, the one thing you realize is there's always going to be surprises [yeah] and I think we just have to, I think we basically have to make sure we have our eyes and our ears open a lot. [yeah, okay] Anyway.

(unpredictability of the job)

M: What I'd like to ask you to do now is if you wouldn't mind just taking a read over these questions and crossing out any that you do not feel are relevant or appropriate for the Phase I oncology clinical trial setting.

S20: Causality in Phase I [reading questions] What, I cross out

M: Anything you don't think is relevant [okay] or useful for assigning causality. Specifically thinking about Phase I or early oncology clinical trials. Fell free to think out loud.

S20: Well there's just one, did the reaction reappears when placebo was given? [mmm hmm] that's a bizarre question, [yeah in the early stages] I wouldn't even think [cross it out if you don't think it's] well, that are not relevant. Well it's not really relevant, whether a patient gets placebo or not I don't think should impact on causality [right] that's just a red herring. Um, was the drug detected in blood or other fluids in concentrations known to be toxic?, could be relevant. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?, that's possible. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?, ah, that's causality potentially. Was the adverse event confirmed by any objective evidence? So the patient was dizzy, then it happened in the clinic or say in the chemo suite and the patient was dizzy and they took their blood pressure and it was way down, yeah that makes sense. So I guess the only one I would cross out would probably be six. [okay]

M: Okay, and then of those remaining ones, would you be able to sort of rank them in order of importance. So what you feel are higher levels of evidence versus less important.

S20: So put the number beside these?

M: Yeah, 1 would be least important and I guess 9 would be most important.

S20: Okay, well this is going to be tough, ah, let's go my most important first, let's see. Um, should I start from 10 and work down [sure] or go from 1 to 9 [whatever you like, whatever you're comfortable with] alright. Um, I think did the adverse reaction reappear when the drug was re-administered that would probably be a 10 [mmm hmm]. Did the patient have a similar reaction to the same or similar drugs in any previous exposure, that's probably the next most common one. And 8, was the reaction more severe when the dose was increased or less severe when the dose was decreased is probably the next important. Um, did the

reaction improve when the drug was discontinued or a specific antagonist was administered, ah, I guess that's 7. Did the adverse reaction appear after the suspected drug was administered, that's probably 6. I'm not sure where to put was the adverse event confirmed by objective evidence because most of the stuff I would say would be ah. Trouble is objective evidence, it could be, so they're talking about something that's kind of I guess observed or was a lab test which could be related to the treatment or disease or something else. So I would put that probably in the middle somewhere.

M: Yeah, I know it's sort of a vague term, objective evidence. I tend to ask people what they think that means because [yeah] it wasn't clear to me when I first read it either.

S20: Um, are there previous conclusive reports on this reaction? I would probably, I put that lower down mainly because I'm more concerned about what I'm seeing in the patient, so I put that as a 4. Um, are there alternative causes other than the drug that could have caused the reaction? perhaps the question is not relevant, it's not saying it's definitely associated with causality it's just for the relevance. Ah, okay, probably put this as, yeah, I'll put this as 3 and put this as 2, okay. [alright, good stuff, great]

M: Sorry I know that's taxing for a Friday afternoon [laughter] Actually this was developed by a researcher named Naranjo and ah, as an algorithm to help clinicians when deciding causality. Did you do, had you ever seen this before?

S20: No.

M: No. Do you think something like this might be useful if you sort of had this as a you know, to run through when you're assigning causality? You can be honest, you won't hurt my feelings. [laughter]

S20: I think basically it kind of intuitively we kind of think about a lot of this already and even though I may not have mentioned all the keys points in this but I think about that anyway. [yeah] Um, it might be helpful for someone first doing clinical trials, but if you've basically got a little bit of experience under your belt this is probably something we do anyway. [yeah, okay that's good to know] **(use clinical judgement)**

M: Then lastly I would like to ask you about any training you've received with respect to assigning causality to adverse events. What sort of training?

S20: Nothing formal.

M: Nothing formal. What about anything informal, anything you can think of?

S20: I worked, well I worked, it didn't have anything really to do with causality but I did do a Fellowship for a year with NCIC Clinical Trials Group. But that wasn't really related to that much to this. Um,

M: So how did you figure it all out, how did you learn how to assign causality?

S20: I think we basically um, I think we work with our clinical research associates and nurses and we, we um, I think we attend NCIC Clinical Trials Groups meeting. We go to oncology meetings where um, there is discussions on Phase II trials. Ah, we read oncology journals. So I think its basically picked up, maybe have a discussion occasionally with our colleagues.

M: What do you, like when you're discussing it with colleagues, what are you usually talking about there? That's not how you, did you learn from each other?

S20: Well I think, that's kind of, I don't think that happens on a regular basis but if you have a situation where, that's really bizarre I mean, and um, I'm just trying to

think, um, well there may be something for instance that somebody may not be totally aware of. But say somebody, and this hasn't happened to me personally but you could argue about, but somebody's head and neck protocol and they were getting an infusion of 5-FU with a study medication um and they were having severe chest pain. And gee could this be related to the study drug and what's going on and then you might see well infusional 5-FU can be associated with coronary artery spasm. So maybe it's, you know, so how do you assign causality there? So you go well it's possible it's related to the 5-FU infusion or the study drug. So that's a tough one because it's serious enough you really don't want to expose the patient to this again, it could cause severe symptoms. So what do you do, do you drop the 5-FU and continue with the study drug or do you just drop everything? And that would probably, that's something that sometimes you might, it's tough, but you might have to say okay, maybe I should discuss this with the medical chair of the study because you just can't make a decision. [yeah] That's a tough one. [yeah, sounds like it]

M: What additional education about assigning causality if any, do you feel should be made available to clinicians? Do you think there's a need?

S20: Yeah, I think it would be very interesting to do an experiment where you had a clinical scenario. Ah the patient is on, say a study drug where you could develop a profile, here's the animal toxicology, here's the medical status of the patient before going on the study, the type of malignancy. And present a scenario that the patient has developed such and such side effects. And it would be very interesting to see in that scenario with experienced clinical investigators and also say um, people who have just finished their residency program in medical oncology and fellows and um, maybe nurses. How would they ascribe causality to such and such an event. I think it might be an interesting eye opener. I suspect that's been done, maybe that's why the survey is out there, I'm not sure. Have you seen anything published? [no] Neither have I. So it might be a bit of an eye opener, it would be like the scenario of what was done 20 or 25 years ago at

PMH and I think a couple of other places where they had okay, how good are we at assessing response rate? And you had a bunch of different size metal balls that were covered with foam and you had the residents and the experienced clinicians measure these balls and found out how much a discrepancy there was in the measurements. And then measure them later on and find out how many times there was a false response rate when you're measuring the same size ball. [really?] Fascinating data on that.

M: Okay so, PMH, that was a study done at PMH?

S20: Yeah, I think Ian Tannock was involved in that probably about 25 years ago and I've seen that replicated somewhere else a few years later.

M: What was the last name [Tannock].

S20: And, and ah, basically I think opened a lot of clinicians eyes that you know, our, our ability to assess response rate, we've got to be very careful, especially with smaller lesions where there's more margin for error. [mmm hmm] And, and you know, I think we have to take response rates as an endpoint in terms of making decisions about the effectiveness of treatment with a grain of salt there may be harder outcomes that, that may be more appropriate to look at. And the response rates are only one bit of information that we should be looking at. [yeah] **(feels the need to be very cautious when attributing causality)**

M: And that was in breast, was it in breast?

S20: Um, this was you know, this was not breast cancer, this was basically different size metal balls [right] this was just a simple experiment [could have been a tumor anywhere really right?] yeah, yeah. [okay]

M: I'm going to look that up, that sounds good. Okay and how did they, you've peaked my interest now, okay, I'm going to look that one up. Was that done at like a medical conference or something.

S20: This was, if I remember correctly it was published in one of the first issues of the Journal of Clinical Oncology.

M: Yeah, but how did they actually get all of these investigators, they must have something to do with a conference or something.

S20: No, it was, I think it was a bunch of clinicians and residents at the Princess Margaret Hospital and they had a room where they had these balls covered with foam and you had to go around and measure them. And, and they probably had maybe 10 or 15 people do it. [yeah] And then they came back, I think they came back maybe a day or two latter and remeasured and said okay let's see how you measure up.

M: Excellent, that's good, simple but to the point. Okay, great, well those are all the questions that I have for you. [That was relatively painless] Good I'm glad it was. [hope it wasn't too painful for you].

Subject 21

M: I will just explain a little bit about what it is that we're doing. [mmm hmm] We're interested in the way investigators assign causality to adverse events, in oncology, early Phase oncology clinical trials. [sure] As you know, many groups such as industry sponsors, clinical trial cooperative groups and research ethic boards, all expect prompt and sensible causality assessments. But it's not always that straightforward and if done poorly can have large implications. So we're interested in developing a tool to help clinicians efficiently and reliably assign causality during Phase I oncology clinical trials. And we feel that by better understanding your needs as a clinician, we can make this tool more relevant to you. [mmm hmm] So, do you have any questions? [No I don't think so] So first

we'd like to get a better understanding of the thought process that you use when assigning causality for adverse events. So let's say one of your patients in an early Phase I oncology clinical trial experiences an adverse event and report that to you and you have to assign causality, let's say it's a serious adverse event. [mmm hmm] Can you just walk me through how that situation is handled and what your thought process is when you're assigning causality?

S21: Sure. So I make sure that I'm aware of the potential adverse effects that have been described previously reported, like in the investigators brochure or in previous Phase I trials. And then I also look at the disease the patient has and whether or not the disease itself could have been responsible for the SAE. And then you know, if the patient has received any other interventions.

M: Any other interventions like other study medication or?

S21: Or if they'd had radiation or if they had a procedure like a biopsy or something that could be responsible. [okay] So I guess first I would consider the drug, you know it's mechanism and the reported side effects.

M: And where do you go to get the information about the mechanism of the drug?

S21: Usually back to the protocol and to the investigators brochure. [okay]

M: And do you always refer back to the protocol and the IB when you're assigning causality?

S21: I can't say that I always dig it out but sometimes you know that you're working with drug X and you know that similar drugs have caused certain SAEs before. So sometimes it's just my memory of, of what is likely to be an adverse event with that drug. And then if its a less common side effect that I wasn't particularly expecting then I would go back to the IB and to the protocol and see

if there was any evidence for that from previous work. **(only uses IB for uncertain situations)**

M: Are there any other resources that you use when you're

S21: Oh sometimes I look on ASCO.org or

M: What are you looking for when you go there?

S21: Well I'd look at previously published abstracts on ASCO.org and see if there are any other Phase trial, Phase I trials and see if the SAE that I'm looking at has been described previously. [okay] Sometimes I just go to Google [laughter].

M: That's great, a lot of researchers use Google. Yeah, it's a wonderful tool. Okay. Are there any tools that you use when you are assigning causality like flow charts or algorithms or decision trees.

S21: No, just what knowledge I have in my head and in the IB and sometimes on the net. **(use of clinical judgement)**

M: Do you think a tool would be helpful?

S21: I do as long as it wasn't, didn't take a long time to do, that's the bottom line. [laughter] As long as it wasn't too complex. **(time constraints)**

M: What are you thinking of when you're thinking of the complexity of it like?

S21: If it was more than one page I would be unlikely to do it. [okay] Because there's already a lot of documentation required for early Phase Clinical Trials. And ah, you know, if I thought it was truly helpful I would do it but if I saw it as just

another piece of paperwork I probably wouldn't do it. [yeah, yeah, okay]
(overwhelmed with paperwork)

M: Are there any other criteria that you think, you know, for this tool, do you think it should, what other?

S21: I guess it would have to be fairly general to be able to extrapolate it to every possible SAE and every possible drug and disease. [yeah]

M: I suppose it would either have to be really general or it would have to be um, very specific and individualized.

S21: Right, exactly.

M: Are there any general guidelines that you follow when you're assigning causality?

S21: No, it's kind of, for me it's like an intuitive process, and I should also say that sometimes the CRA's do it. [okay] And actually in fact, just very recently in the past month or so we changed our reporting forms here so that they never used to have a column for attribution and now they do. So now that it's on the form that I see in the clinic, I'm more likely to fill it out. [oh I see] Whereas previously the CRAs would just come to me if, if an attribution wasn't straightforward [oh I see] and then often they would be doing it themselves.

M: And did that cause problems at all or?

S21: No, I probably wasn't thinking about attributions as much as I should have been. And part of that's because I don't do any Phase I, I just do Phase II so you know, attributions are more important in Phase I than they are in Phase II when

the toxicities have already been described. And so just because of the trials that I do it hasn't been as much in the forefront of my mind.

M: But that additional column in that [makes me think of it more] chart, makes you [yeah].

S21: Yeah, the way the form is set up now it will say, it will have the CTCAE or whatever that abbreviation is for the Common Toxicity Criteria, you know, it will say rash and it will have graded it from 0 to 5 or whatever. And then right next to that it will say attribution from you know, not at all likely to highly likely or something like that. [okay]

M: Actually I'm going to be talking to one of your CRAs later today and I've asked her if she could show me that chart [yeah] because I've heard good things about it.

S21: Yeah, I think it is going to add something to the accuracy of our data. [yeah, good]

M: What I would like to do now and just ask you to consider a scenario for me. [sure] So let's say you're treating a 65-year-old female patient with a confirmed diagnosis of metastatic breast cancer. [mmm hmm] And she is in a, let's say she's in a Phase I clinical trial with a new investigational drug when she experiences a pulmonary embolism. [mmm hmm] How would you assign causality to the study drug if there was a 75% chance it was due to the study drug and a 25% chance it was due to all other factors, say disease progression, adjuvant treatment, concomitant illness, concomitant meds.

S21: I would probably mark that as probable.

M: Okay, and the scale would be certain, probable, possible or unlikely.

S21: Probable. [probable, okay]

M: Why is that? Just because you think that [75 is] pretty high [yeah].

S21: Yeah, I mean it's not certain but it's more than likely, more than 50/50 so.
[yeah, okay]

M: And what if it was 50/50?

S21: Then I would say possibly.

M: And what if there was a 20% chance that it was due to the adverse event and an 80% chance it was due to all other factors, or sorry due to the drug?

S21: So, I'd say less likely or unlikely. [unlikely?]

M: I'm just trying to get a sense of how people understand those terms and you know, trying to link some percentages [sure] and probabilities to that because. And I know in a real life situation you would never probably have those probabilities but just to try and understand how people interpret those terms.
[yeah]

M: What would you say are some of the problems or challenges with assigning causality?

S21: Just that there's more than one possible explanation for a lot of toxicities that you see. So as you say, PE can be due to the drug or it could be due to the cancer and maybe they would have had that PE even if they weren't on the drug or because they're immobile or any number of factors. I guess it's just that there are multiple factors at play. I'd say that's the most difficult aspect of it.

(uncertainty is the hardest part) And plus the fact that they may be on other treatments, like they may be on something for their hypertension or their diabetes [yeah], they've got often multiple medical problems aside from the cancer.

M: So it's pretty complex. [yeah] Are there any other challenges you've encountered with assigning causality? Maybe even just like logistical or um?

S21: Just the kind of 'pain in the ass' factor [laughter] the paper work, that kind of thing. [yeah, okay] **(hates paper work)**

M: So it's just sort of one other thing that you have to do.

S21: Or if it's a totally unexpected new toxicity and sometimes that hasn't really been described in the IB or previous Phase I trials and you don't know whether or not that was due to the drug if it hasn't previously been described.

M: What do you do in that case?

S21: I think about the mechanism of action of the drug and make my attribution assessment from that. Or sometimes you know, like if the toxicity is severe then you'll stop the drug and if the adverse event abates then you'll have to conclude that it was the drug.

M: Sometimes you have to attribute your causality and then you stop the drug but you've already made your causality assessment and you don't yet know what [mmm hmm] is going to happen with that patient, you don't know the outcome. [right]

S21: I guess you may have to go back and modify you're attributions.

M: So you've done that before?

S21: I probably did that in Hamilton but I don't think I've done it here. And that's probably because up until very recently the CRAs have been doing almost all of the attributions. [right]

M: Any other problems or challenges that you've encountered with assigning causality?

S21: I don't think so, like on the whole like most of the adverse events that I see have been described in the IB or in previous trials, so if I have them on a tyrosine kinase inhibitor and they get a rash well that's expected. [yeah] So most of the time it's not rocket science. [yeah, that's nice]

M: What are your concerns about how clinicians currently assign causality?

S21: I probably don't give it as much thought as, as I should. **(feels they could put in more of an effort)** I mean, I guess the real risk is that if people are falsely ascribing SAEs to the drug when it's really the cancer then you could potentially throw out a good drug.

M: So why is it that you just don't give it as much thought as you should?

S21: Probably because up until recently it hasn't been on the form. And also because you know, I don't do Phase I trials here, so you know, it's not, it's not the primary endpoint of the trial. It's not to describe the toxicities it's to describe the response rate so you know, it's kind of a secondary thing to document the toxicities for most of the trials that I do. [yeah] And you know when I was in Hamilton I was doing Phase I trials there then obviously it's more on your mind. And also because the nurses there would come to me and ask me to do the attributions [yeah, yeah] but not so much here because we're not doing Phase I trials here.

M: Now you said that obviously if you were to over-assign causality there's the potential to throw out [mmm hmm] potentially a good drug. Do you have any examples of you know, when that's happened in the past?

S21: Oh, for instance maybe you could see a problem, I can't think of a specific example in the past but I could foresee that maybe you know, you might throw out a drug if you saw an abnormally high rate of pulmonary emboli or something when that's something that's going to happen with cancer anyway so that could happen. And I guess the converse is true too that if you don't, if you don't adequately report the toxicities then you might be introducing a drug to the market that is dangerous. I mean I guess you could look at the Vioxx example for that, you know, maybe there was under reporting of cardiovascular incidents with Vioxx in the beginning. Because probably everybody said oh well, all these patients are old, they have arthritis, they're old so and old people get strokes and heart attacks so. And then it was only when it had been on the market and millions of people are taking it that you see that event. [mmm hmm yeah, that's a perfect example isn't it]? You know, I have a particular concern for one drug that I'm using for kidney cancer that I've seen a lot, a lot of really negative outcomes with it. And yet when I look at the data that is on you know, the ASCO website and I even have written to the PI of the trial saying you know, my impression of this drug isn't all as safe as what it's cracked up to be.

M: What drug is that? [sunitinib] Good, alright so those are your concerns then, that you could potentially throw out a really good drug or on the other hand you might introduce a new drug to the market that is not [as safe] as safe as originally thought. [yeah] Any other concerns about how clinicians assign causality?

S21: I guess the other thing is that you know, sometimes a drug is safe if given in the study, in the right population, you know what I mean. I'm thinking of the sunitinib example of that, you know, I've had some really bad outcomes with that

drug and I think maybe my patients weren't the right, you know, their performance status was too bad. Maybe that was my fault, that I was trying to extrapolate data from a study to a general population and you can't do that. I think maybe you know, if attributions were, you know, if that was more a focus then I would have said, alright this is a dangerous drug. I don't know if I'm making a lot of sense. **(Fears being individually blamed for misattribution and the consequences that may arise)**

M: But then on the other hand right, I mean once this drug does hit the market and becomes available to everyone [yeah] there will be people receiving it [yeah] that maybe shouldn't or don't have the greatest performance status [exactly]

S21: Yeah, that's my concern that, that particular drug was only suitable for fit patients [yeah a very clean study population] Yeah, and when I tried to use it in my kind of borderline patients well they definitely died early.

M: And that was kidney cancer patients? [yeah]

M: What external influences or pressures from third parties have you felt when assigning causality?

S21: Yeah, that's a very valid question, sometimes I will have a patient who is having a serious toxicity and I want to stop the drug and the patient is pressuring me to keep on the drug. And you know, if you are going to keep them on the drug then maybe you have to under report the toxicity. **(new perspective-patient pressures)**

M: Okay, so the patient wants to stay on.

S21: Yeah, I've had that happen several times that the patient does not want to discontinue the drug even though they've got substantial toxicity.

M: And then you mentioned that, that might cause you to want to under report [yeah] toxicities thereafter.

S21: Maybe I call it a grade 2 when it was really a grade 3.**(change grading of causality attribution to suit the demands of the patient)**

M: So that's to do with um, that's to do with the severity. [yeah] What about your causality assessment would that sort of change at all?

S21: No, I never really tinkered with that.

M: Have you felt any other external influences or pressures?

S21: No, I don't, I don't think so, no, it's mainly the example I can think of is patient's pressuring me to keep them on a drug when I'm not sure that's to their, you know in their best interest.

M: So, we talked a little bit about this, so from your perspective what would make assigning causality easier? You know, we're going to try and develop this tool, but is there anything else?

S21: A cleaner patient population you know [sorry?] a cleaner patient population [yeah, making] that's never going to happen but if you had a patient that wasn't as at high risk for PE or for a decline in their functional status or whatever then that makes it easier to say that it's the drug. If they were quite fit when they came on the drug and then something happened, it's probably the drug.

M: And unfortunately we're usually testing these drugs in [yeah] metastatic cancer patients right.

S21: Other than that, I can't really think of anything.

M: What I'd like to do now is ask you to take a look at this algorithm that was developed by a researcher named Naranjo. [mmm hmm] So there's 10 questions there, he developed this algorithm to help clinicians assign causality to adverse events. I was just wondering if you wouldn't mind crossing out any that you do not feel are relevant to the Phase I, specifically Phase I oncology clinical trial setting. So if you don't think they're useful or relevant, just cross them out.

S21: I think they're all relevant.

M: Okay, so now would you be able to rank them for me, so 10 would be most important [okay] and 1 would be least important, so just sort of in your order of importance, what you think?

S21: So does there have to be one, can there be two that are marked 10 [oh sure] or are they supposed to be 1, 2, 3, 4 [no, if you would like to do it that way that's fine]

M: Okay, great thank you, that's perfect. So I guess the least important then was whether the drug was detected in the blood in concentrations known to be toxic. Why did you rank that one so low?

S21: Because some patients maybe had an allergic type reaction and just needed a small amount of the immunogen to cause a reaction.

M: So it doesn't necessarily have to be a highly toxic level [no] for them to react.

S21: No some patients may have enzyme deficiencies make them more susceptible to the effects of some drugs.

M: And then was the adverse event confirmed by any objective evidence you ranked that fairly low.

S21: Yeah, I have to believe a patient if they tell me that their feet are painful or whatever even though I can't see it.

M: Yeah, that's a good example, yeah pain is a really tough one [yeah] you can only go by what patients are saying. And then most important was did the adverse event appear after the suspected drug was administered.

S21: That makes sense [it makes sense yeah, it can't happen before]

M: Did you have any thoughts, like as you were going through this what did you think?

S21: I thought somebody made this up based on Hills criteria [yeah] isn't that true [yeah, it's very like, yeah, it's a lot like Hills criteria] yeah, but that's about all I.

M: Were there any questions that were missing that you thought should have been here?

S21: Nothing I can think of no. [okay, great]

M: Do you think something like this might be useful as a tool to help clinicians?

S21: I think it yes, as long as it were fairly brief and user friendly and also it depends I guess on the level of experience. Somebody new to clinical trials that would probably be helpful but somebody that already has that thought process engrained in their memory might not need it as much. **(time constraints discourage clinicians from using a tool, which is design to help them)**

M: Yeah that's what I think too and I've received that feedback from other people too that it would probably be good for somebody just starting out. [yeah]

M: So lastly I would like to ask you about the training you've received [sure] specifically with respect to assigning causality to adverse events. So have you received any training?

S21: Zero. [no eh]

M: Not necessarily formally, but informally?

S21: No, the first time I had to do it was when a nurse came to me and said you've got to do this [laughter] [and how did you even know how to do it] I said, are you sure that's my job? [laughter] So I mean it was just kind of logic, you know, in my mind I guess I was using something like your checklist, you know, looking for a temporal relationship and a dose response relationship. You know, and a biological plausability relationship.

M: Right, so you recalled your Hills criteria. [exactly] [laughter] And where did you learn about the Hills criteria?

S21: In my epidemiology course [in the epi course you took at Mac?] Yeah.

M: But not all MDs get that do they?

S21: No, most wouldn't no. But I mean, I think there's a certain logic to it you know, I think everybody, anybody is going to know well it's not the drug if the reaction happened before the drug. [yeah, yeah] And anybody's going to conclude that it's more likely the drug, if you stop the drug and the reaction calms down. I don't think you, I think you can kind of describe what you're thinking

better if you know about Hills criteria but you don't necessarily have to have that teaching to reach the same conclusion about causality. [yeah]

M: What additional education about assigning causality do you feel would be helpful to clinicians?

S21: Well you know, I guess like something like running through that checklist would be helpful, particularly as I said to somebody who is new to the process.

M: Is there anything else that you can think of that might be helpful in terms of education?

S21: I guess, I keep coming back to this, but keeping it simple and brief because there are a lot of competitors for a trialist's attention, you know, like there are a lot of time constraints and something more simple that would be best.

M: I know, you guys are super busy. Okay, I think those are all the questions that I have for you then. Do you have any questions for me?

S21: Yes, I'd like to hear how it all turns out.

M: Yes, definitely, so the plan is once we analyze all this interview data we will be sending the participants an executive summary [oh that would be good] of the results. And we're also hoping to present at the fall NCI meeting although I'm not sure, it might end up being in the Spring [yeah]. We would like to present at an NCI meeting. [yeah that would be interesting] Yeah, yeah, I think, I think there's some good stuff coming out of these interviews for sure. Okay and so do you have anything else you would like to add?

S21: I don't think so. Good luck with your project.

M: Thank you very much for your time.

Subject 22

M: Even the most experienced clinicians find assigning causality to adverse events challenging. Many groups such as industry sponsors, clinical trial cooperative groups, research ethic boards, all expect prompt and sensible causality assessments. But I'm sure as you know, it's not always that straightforward and there are implications. [mmm hmm] So we're interested in developing a tool as I mentioned to help clinicians efficiently and reliably assign causality to adverse events that have occurred in early Phase oncology clinical trials. And we feel that by better understanding your needs as a clinician, we can make that tool more relevant to you. [okay] So, do you have any questions? [No I think I understand what the study is about] So first I'd just like to get a better understanding of the clinical reasoning, the thought process that you use when you're assigning causality to an adverse events. So let's say one of your Phase I or II patients comes in and reports experiencing an adverse event, let's say it's a serious adverse event. Can you just walk me through the thought process that you use when you're assigning causality to that event?

S22: So I think the first thing obviously is to describe the event, you know, how severe, exactly what it consisted of, is it something that's well recognized, is it something that's entirely novel or unusual? The next thing I think is to look at when it occurred with respect to going on the study, did it occur before starting, you know, is there evidence that this was kind of brewing prior to starting the treatment? [okay] So we look at the temporal association, we look at the, you know, the course of what happened. Did the patient stop the drug? For instance, if it's an oral medication that he's taking continuously he would have the opportunity to stop the drug and then see if it got better. On the other hand if it's a kind of one off, intravenous every 3 weeks kind of thing then the patient doesn't have the opportunity to stop the drug. But sometimes if it's oral, and increasingly these new drugs are oral, they may phone up and say hey, you know, my tongue has turned blue what do I do you know? And the nurse is going to say well gee

maybe you should stop the medication. So you may have temporal evidence about what happened depending on if the patient stopped the drug or not. [yeah] So I guess this is kind of the initial process, just to describe the event, try to work out a temporal association between going on the trial and maybe stopping the medication. **(cope with uncertainty by placing a strong emphasis on temporal association)** Restarting it and seeing if it comes up again you know, that sort of thing, trying to look for cause and effect relationships really.

M: You mentioned trying to understand if it's well recognized or if it's something that's novel [right] how you do determine that?

S22: Well we have a, everyone that goes on trial here has a PAR form and that stands for patient something, something report form, patient adverse event report form or something. But basically it's a series of standard common side effects or adverse events which are kind of stereotyped you know, diarrhea, mucositis, neutopenia, rash, hand-foot syndrome, vomiting, nausea, that sort of thing. So there's a whole list of these things, which most adverse events that are related to drugs will fall into. However if something novel occurred like for example, this occurred this morning where somebody got ocular irritation, he was on a drug, a drug combination that was novel this was, this is not something that you see all that commonly and as a result it's not on the PAR form. So it has to be recorded separately on the back of the PAR form where there's space for the CRA or the nurse to write this kind of stuff out if it doesn't fall into a simple category. You know, like diarrhea grade 2 or something, something that's unusual or novel our system allows the nurse or the clinical trials associate to write it out on the back so that firstly there is a permanent record of it. And secondly it alerts me to the fact that something, a) something's happened and b) that it's not the usual kind of thing. [mmm hmm]. And then it becomes difficult for me, but then you're forced to make some kind of a decision. **(feels a decision must be made- feels forced, very hard to do- complexity and uncertainty of the situation)**

M: With respect to what?

S22: To the causality [oh the causality yeah] because you have to react in some way. So I had to think this morning for example this ocular side effect, was it due to you know, drug A or drug B or the combination. Or was it due to something incidental like you know conjunctivitis or something. So you have to think about alternative causes, alternative explanations. I mean people with cancer get many symptoms from the cancer that are not necessarily due to the drug, they may just be due to the underlying disease. And of course a lot of people have comorbidities because they're elderly and have a 101,000 things wrong with them. **(almost too many confounding variables to deal with)** And you know, is it just something incidental. So I think one of the important things in the causal reasoning is, is to be aware of what the possible causes could be. You know, it's due to the experimental drug, it's due to some other drug the patient may be taking or may have just started taking. It could be due to the underlying cancer, it could be due to some other illness that may have occurred or that may have already existed like diabetes or angina or something you know. So I think critical in the sort of, the kind of cognitive approach is the realization that there's a whole slate of things which could possibly either alone or in combination have resulted in this phenomena. **(have to have an open mind, be open to possibilities)** [right] On the other hand you don't want to be paralyzed by uncertainty because if you're in a busy clinic you can only tolerate paralysis for so long [right] you have to make some kind of a decision. **(time constraints)** So that's

M: So in that case, what did you?

S22: I would say 95 to 98% of the things that happen, it's, you know, it's kind of, to an experienced clinician you know, without wanting to entrench, you know and have my own prejudices confirm themselves. **(uses experience to cope with uncertainty)** But I think that. My sense is that 95 to 98% of the things that the so called toxicities or adverse events we can generally, going through this kind of a

process make the correct kind of attribution. But every now and then it's tough, like what happened this morning for example, it was difficult, it wasn't clearly obvious to me what was going on. **(some decisions are very difficult, even for the most experienced clinicians)**

M: And so what did you attribute, what was your attribution in that case?

S22: Well I thought at the end of the day that it was likely due to the drug, so without specifics ...

M: And what was that based on?

S22: Without going into the specifics, the patient was being treated with two different types of drug. One is a common chemotherapy that's been used for years and the other one is a novel drug that's also been used but has been used separately as a single agent.

M: So this was the first time it was being used in combination with the chemo.

S22: In combination, exactly right. And so it was this unusual ocular side effect which has rarely been described before with the chemotherapy, the old fashioned chemotherapy but not commonly. And has been described with this novel drug but not quite in the same way. So my sense is that it's probably something to do with the two of them together. [right] But certainly I think the novel drug was necessary. You might argue you know, causality is difficult, causality is not simple. [no] You know, there's different kinds of causality, there's the kind of relationship where something is sufficient on it's own. [right] There's another kind of relationship where something by itself is not sufficient on it's own but it's necessary. [and then there's] And there's relationships that are where you have it's neither sufficient nor necessary but it nonetheless contributes. **(verifying types of causality make the decision even more complex)** So it's actually, on

the one hand you're saying well just attribute causality but there's actually a more profound and fundamental understanding of causality with respect to well what type of causality? Um, which is important I think because it does help you manage the situation you know, so sometimes I don't think it's possible to be 100% sure. Except I think it's usually possible to be reasonably sure that a drug has got something to do with it. [mmm hmm] But I think at the end of the day you may just have to reconcile yourself with you know, an attribute of say probably as opposed to certainly. Because it may not be possible, it maybe kind of fatuously accurate like you know, what's the distance between here and Ottawa or here and Hamilton, well it's approximately 160 kilometers. But there's no point in saying it's 161.2357 kilometers it's kind of speciously accurate you know what I mean. [yeah] So I don't think that we should attribute causality more than we can, you know because we feel some obligation you know, to fill in some category in a form. **(feels obligated to make a decision, even in cases of uncertainty)** So I think an intelligent approach doesn't demand that you be more accurate than you can. Because I think I've been in some situations where it doesn't, you know it either is or it isn't and it only gives you two possibilities. You know, this is caused by drug X or it's not. And in a sense I don't like that because, I know, I just don't think it represents the reality and the reality is sometimes there is an element of uncertainty. And I think that the best kind of, the best kind of forms that you have to fill in, when you fill in these, allow you to designate if there is some uncertainty or not. [right, yeah]

M: That was actually one of my questions, yeah, so you definitely prefer to have sort of the gradation rather than

S22: Yeah, I prefer the gradation and having said that I mean, I think the gradation is, is not the end of it, I think it's perhaps the beginning of an intelligent insight into it. But I don't think that, you know, in terms of what we were talking about where something might be necessary but you know, the necessity and the sufficiency of it. I'm not sure that, that emerges immediately from, from a kind of

graded scale. So the kind of graded scale if you like, where you're on the one hand on the one extreme you are certain that this is not due to the drug, on the other hand you are certain that it is due to the drug. But then in-between you've got, you know, possibly and probably. I mean the simple thing would be a 4 point scale where it's definitely not, possibly is, probably is and definitely is might be. But you know even once you fill that in to the best of your ability you don't really know whether the, what the, you don't really have a lot of insight into the precise causal relationship. [mmm hmm] You know, whether the drug was just one of the factors for example that led to the event. [right] **(type of causality is most difficult)**

M: So for example in your case where you think that it's a combination of the chemo with the drug, not just the study drug on it's own. That's really not reflected when you're attributing causality is it?

S22: So I say for example, if I had to put down on the thing I would say that this is probably due to the new drug. But that doesn't give you any information as to the fact that probably the other drug contributed something. [yeah] And that probably if we reduce the dose of the novel drug that you wouldn't get this problem. [right] So that not only was it due to the drug, it was due to the drug being delivered at a certain dose, so, you know what I'm saying. [yeah] So an in depth understanding of the causality, let's say for example, let's say in this case the ocular toxicity was due to the presence of the other drug, plus this new drug given at a certain dose. And that we could do, in order to get rid of it, which is really what you're trying, the whole purpose of this is to get rid of the toxicity, you could do one of two things. You could get rid of the, the old-fashioned chemo drug, that might solve the problem. Or you could keep the chemo drug in and lower the dose of the novel drug which is what we elected to do. [right] And both of those things might actually solve the problem. So in a way what we are getting at here in studying causality in-depth is what is the strategy we have to adopt to get rid of the problem? Because when you successfully get rid of the problem in a way you

might just be trying things on an ad hoc random empirical basis. But if you stumble on some strategy that gets rid of the problem [mmm hmm] it does give you, not total insight but more insight into the precise nature of the causality. But, but even if you stumble on a strategy that's effective it doesn't necessarily mean that there aren't other strategies that are also effective. [sure, yeah] So this just speaks to the complexity of this, especially when you're dealing with two drugs. You know, if you're dealing with one drug it's somewhat simpler but I think you know, you may want to address this in the tool, when you're dealing with two drugs, which I think is often the case in oncology, two or more drugs it then becomes quite important to but also more difficult to understand the precise causal relationships that are operating. [yeah, definitely] And I think, we're in a situation quite often in oncology where you have mild to moderate, let's say ocular toxicity, it's not life threatening but irritating and it definitely impairs quality of life. [yeah] But it may not be a sufficient priority of the academic community that they will specifically design trials to sort this out. But in fact you may need to design a whole lot of different trials, or at least different strategies to sort out these kinds of you know, low level irritating toxicities. Such as for example, the hand/foot syndrome with a drug called capecitabine, which is not life threatening therefore people will say well let's throw in some peridoxine or maybe try some dose reduction. Dose reduction always works but you know peridoxine is felt to alleviate it but nobody really knows for sure because it hasn't been felt to be a sufficiently high priority to actually design a proper study to, to evaluate peridoxine. So you just don't know you know, whether, if you do dose reduction plus peridoxine, it seems to kind of get better, was it the peridoxine, was it the dose reduction? If you gave the peridoxine maybe you don't have to have a dose reduction and that would be you know, potentially quite an important piece of information. **(trial and error in trying to eliminate toxicity)** But because this is not regarded as the most, as the highest priority of the academic community, you know. Despite the fact that capecitabine has been on the market for 5 to 7 years we're still in the situation where we don't really know how to manage [what's the best] what's the best strategy of what in fact is the commonest side effect of

capecitabine which is the hand/foot syndrome. So we don't know, you know, we just don't know.

M: So definitely dealing with two or more drugs in combination is a challenge [yeah] in terms of assigning causality, are there any other challenges?

S22: Well I think you know, part of the problem is that um, some of the toxicity is pharmacogenomic, you know, is based on individualized differences at the genomic level which we're not aware of you know. So firstly, we know that these genomic differences exist but we don't really know because they aren't measured so we don't have the information available to us. **(lack of resources)** And also what may, what may be important is genomic differences that exist that we don't, which we don't know about you know. Single nucleotide polymorphisms with respect to genes that may affect you know your skin or your bladder or your brain or something that are hidden from us right now because we just don't know that they exist. [mmm hmm] And you know, obviously you know, the whole western tradition of thinking is mechanistic thinking. You know, we don't believe in magic, we don't believe in, I mean quantum physics is a challenge to the western mentality because it seems that at a quantum level [requires a leap of faith] things happen without any immediate cause. You know, a radioisotope decays, we know that statistically you know the half-life of plutonium maybe 60 years or 100 year, whatever it is, or 1000. I don't know what it is but you know that at 1000 years, let's say it's 1000 years half of the plutonium atoms that are going to decay will decay in 1000 years on average. But you don't know on a Tuesday afternoon at 3:00 [how many] what one is or isn't [yeah]. Because it seems to be inherently unpredictable which is an affront to the western way of thinking. But at the level of toxicity you know, we have a sense because of the way we think and approach science that everything at this kind of level, at the macroscopic level is explicable. [yeah] We, we know and this is really one of the things that drives us and irritates us is that we know that there had to be an explanation why Mr. xxx got 3 grade diarrhea five days after starting his chemotherapy. You know, there is

a causal chain of events and it's not random, it's not unpredictable but we just don't know enough about it to predict. So one of the things that interests me for example, is the prediction of toxicity. I actually have a website called www.predictpatientevents.com [oh really] which makes available to functioning clinicians through the Internet mathematical models which just require parameters being put in for say anemia in ah, in the adjuvant treatment of breast cancer or the advanced non-small cell lung cancer setting. With nausea and vomiting across a range of different disease situations, chemotherapy-induced diarrheas, the latest one we've put up about two weeks ago. So you can input data um, parameters with respect to age, gender, you know, line of treatment, so on and so forth that we have just empirically found to be associated and predictive of chemotherapy and have this updated cycle by cycle. So that you can get a report that you can share with a patient that in a way might look like a weather report saying you know, the risk of precipitation this afternoon is 53% and you can decide what you're going to do about it. [right] But we give you a prediction on a percentage basis of you know, significant grade 3, grade 4 diarrhea associated with this cycle of chemotherapy with either say FOLFOX which is oxaliplatin, 5-fluorouracil and leucovorin or irinotecan, which is a regimen called FOLFIRI. So we're able to do this and we think that these um, this kind of prediction system is significantly better than, than a crap shoot than a random you know, it may or may not happen kind of thing which really happens now [yeah] it may or may not happen. So that, I mean, our belief is if you know with a greater degree of certainty whether or not you are going to get serious toxicity that you can do something about it before it happens. [yeah] So we're interested in explanations as well but from a slightly different point of view because we're interested in identifying um, parameters if you just use a general word that are associated reliably with the presence or absence of some toxicity, such as chemo-induced diarrhea. [right] Now we don't, from our limited point of view, don't really care whether they're causally implicated in the mechanism. But we just want to isolate these things because they're reliable indicators that it's going to happen. So it's like the red sky at night, do you know that? [sailor's delight], so

the red sky doesn't actually cause the weather the next day [no] but it's a signal as to what the weather is going to do next day. And it's obviously related in some deep way to the causality but by itself it may not be the explain, the cause, in the causal chain of events. [yeah] So for instance, your performance status is highly correlated with the appearance of many different kinds of toxicity. Um, but the performance status itself is not what causes the toxicity, it's the underlying physical status of your body that manifests as a performance status. And there's elements of that which cause the toxicity. So you know, we're interested in it here as well but we're interested in the predictive ability of parameters. Now obviously if we can isolate the causal events that would probably, presumably increase the reliability of the prediction. [right] So when, when we look for a model, we look initially for things that might be associated causally. So let's say we're interested in neutropenia, one of the things we would be interested in is how much radiation [have they received] have they received to what percentage of their bone marrow, you know, the skeleton that carries the bone marrow and that casually would be associated with myelosuppression subsequently because you've eliminated part of your bone marrow, therefore it makes sense it would be more prone to getting myelosuppression. But other things maybe unpredictably associated, like you know, your creatinine or your alkaline phosphatase or something it just might come up as a signal and we, we would incorporate it in the model because it's useful. Not necessarily because it's causal but just because it's useful as a flag. [yeah] So we're also interested in this [great that sounds wonderful] so just at it from a slightly different perspective.

M: Wow, yeah, I'll definitely check out your website [check it out]. Have you written some papers about it?

S22: Yeah, there's an article published in Lancet Oncology and several others in abstract and others that are being submitted um, you know that, that you might want to look at. [definitely] We're encouraging oncologists to try and use them.

M: I think that's useful information to give to patients and you can, like you said, maybe try to preempt some of these events from happening.

S22: It's the preemption that we're interested in. So that we think that a lot of the downside of chemotherapy is actually unnecessary [yeah] and that if you knew what was going to happen before it happened [you could take some measures] you could do something about it. [increase your fluid intake say or] Or go on GCSF or whatever, or don't take that holiday to Florida or, there's a lot of things that you might do differently. But one of the things you might do differently is you might give the chemotherapy at a lower dose or you might prescribe a supportive care medication. Or you might instruct the patient on early monitoring and intensify the educational and monitoring efforts. So there's a lot of things that you might do if you knew about it, which right now we pretend in a way that we don't. And you know, we give toxic chemotherapy knowing that up to 33% of people will get serious, sometimes life threatening side effects. But the question is, what makes that ethical? The only thing that makes that ethical is you don't know in any group of 100 patients who are the 25 to 30 patients [who are going to make it], so the whole basis, well who in fact will get ill. [yeah] The only reason that you're allowed to do that, first of all the rationale is you over treat a minority in order not to under treat the majority. I mean that's the only reason why we do it. So, but if you knew that this person was going to get grade 4 diarrhea if you did, if you prescribed it you wouldn't do it. The only reason it's acceptable ethically is because it's anonymous okay, but the minute you knew somebody, this was going to happen to somebody, you would be forced as a, you know good medical practice to do something different. Either lower the dose, prescribe Octreotide, you know, whatever, whatever you know, do something different. So it becomes something important to the whole reputation of chemotherapy and the improvement of chemotherapy in going forward is that we should view it the way the airline industry views accidents, they have a zero tolerance policy basically. [right] So if we had, obviously if you are trying new drugs and so on, some toxicity is going to happen, you can't, but once chemotherapy becomes mature and

incorporated into the standard, there's still an appalling amount of toxicity. And what we should, if we said as a society we're going to have zero tolerance to this, it really means that you have to understand it much better than we do now. **(feels there is still so much to learn in terms of even known toxicities, lack of knowledge in these areas)**

M: And then if you were to add in a novel agent in combination with that chemotherapy it would be much easier to sort out what to do to the novel agent.

S22: Exactly, because it would be much better defined, you know, what, what you would expect [from the chemo] especially by the way if you could individualize the risk. So what our website does is that it doesn't just give you know, like the literature risk it individualizes the risk. And of course in a Phase I study you are dealing with individual patients. So you know, if you got some standard drug plus some new drug, um, somebody gets neutropenia or whatever it may not help you all that much to know that the sort of published literature incidence of neutropenia is you know, 16% because you know, did it or didn't it? you don't know. But it might help you to know that the individualized risk of neutropenia for that patient may have been 1% or 70%. Then you could put the other drug in much better context. [yeah, yeah, interesting]

M: Well maybe we could somehow work together here [maybe, maybe] you never know. Okay, well this is great, I'm learning a ton.

M: What are some of your concerns about the way clinicians are currently assigning causality; you sort of touched on it a little bit.

S22: Well I think you know, they have to make a judgment in a hurry, so there's a concern straight away, they're on the busy machine in the clinic and they have to, you know, somebody puts some form in front of them and they kind of, you know, they've got two pens, one pen in their left hand and one pen in their right hand

and they're hitting the typewriter with their nose and looking at the screen and trying to do four things at once and the telephone is ringing and so on. **(time pressures on top of busy workload)** It really is a zoo as you know, so they have to make hurried decisions, so that's my one, that's my number one concern. Number two is the options that are placed in front of them are different depending on the trial. You know, some trials allow you to, to grade this kind of level of certainty that we were talking about before. Other trials force you to make some kind of premature commitment one way or the other.

M: You mean the options on the actual causality scale?

S22: They maybe limited, this is due to this or it isn't, I've seen that before, that sort of disturbs me. **(disturbing that some scale measures are not flexible)**

M: Well it disturbs me too, actually I think that let's be consistent, how can we expect to be consistent if we don't use the same scale across the board?

S22: Right, that's right, so it's the consistency of the scale that's different. Now, on the other hand, we don't want people, we don't to stop people experimenting with new scales that might be better. But I certainly don't want older scales that are worse. So those are my two concerns just off the top of my head. And the other concern I have is do, are people sufficiently educated in casual attribution?

M: Let's just talk about that for a minute. Um, how did you become educated in assigning causality?

S22: Well I just, I'm curious I suppose about explanations, I'm curious about scientific explanations and it seems to me that the only way that we've really made progress, the best way to make progress is to understand something in a way that an engineer understands something. And I think medicine gets better when, as it turns into engineering. Um, I think it's a long way from engineering

right now and I think a lot of it is gut feeling and kind of intuition. But I think that we will make progress as we turn it from an art into a science and ultimately applied science is engineering. And I think that engineering does mean a very precise understanding of mechanistic relationships if you think about a machine you know um, you know I think um, the things we understand best are machines that we construct and build. And I think we're, this whole enterprise of medicine really is an attempt to reduce the human body to, to a machine in a very, very complicated web of, probably multiple machines at multiple different levels. But really that's what this whole goal, this whole thing is directed towards. **(sees human body as machine)**

M: Yeah, that's, I would agree. So you've learned how to attribute causality because you're curious and you just self-taught or?

S22: Yeah, well I think, if you're interested in logic, you know, it's, it really becomes obvious that there's different possibilities in terms of the causality you know, firstly at the crude level did or didn't? And if it didn't what else did because something certainly did. [yeah] And then you feel obligated as a physician you know, to know why this happened to your patient because even at a non-curious level, even at a functional pragmatic level in order to give people appropriate medical advice, if you really don't have the faintest idea why something happened to them it's very difficult to give them the appropriate advice. **(feels obligated to give patient a concrete explanation, frustrating because there often isn't one)** [that's right] Especially if they're on a drug that might have caused it but on the other hand might also be helping. [yeah] So it's not a trivial thing to say well just stop the treatment. I mean if you're treating somebody for acne or you know, mild headaches or something like that or you know, chronic arthritis. It's very easy to say, stop this anti-inflammatory, stop this topical medication and just see if something gets better because that's an obvious way to do it [sure] from a causal point of view. [yeah] But it may not be quite that easy to do with chemotherapy, even in the, even off trial, but it's particularly difficult to

do that on a trial because you know that you might sabotage you know, the intent of the study by just unnecessarily stopping. You know, I think the onus on an investigator and somebody who's responsible for treating the patient on a trial is quite high really because they have the ability to undermine the trial by making a fallacious attribution. You know because something might have happened you know, they got gastro because they ate something at some restaurant or something and then you say well it's the drug and you take them off the drug. Well then you undermine the whole enterprise you know which isn't just that trial, it stretches back over probably 15 years of work and money and investment. And it's so easy to undermine it by making, by casually making the wrong attribution. **(apprehensive about assigning causality due to serious consequences it can have on the trial)**

M: Do you have any examples of that, like can you think back to a study that was or a drug that had been halted in it's development because of?

S22: I mean I don't you know, you could think about it the other way as well in fact where something happened. Let's say, there is a class of drugs where an incidence of pneumonitis has emerged in lung cancer which was not made necessarily, we didn't necessarily, we weren't, it wasn't immediately apparent to the investigators that this, this side effect might occur. So it's possible that this side effect occurred earlier on but somebody did not attribute it to the drug. So I think, I think it's, now of course you're dealing with somebody people with lung cancer and it's not a surprise that some of them might get pneumonitis and may even die. But you kind of wonder whether somebody thought hmm, this is a little unusual but may not have did, I don't know if anybody did or didn't. But somebody may not have attributed it when in fact they should have. [mmm hmm] So there's two kinds of mistakes you can make. You can make a false positive attribution or you can make a false negative lack of attribution, when in fact you should have. So,

M: Do you remember the name of that drug?

S22: Well it's a drug called Iressa which is a drug that later on it became clear that there was an element of pneumonitis, now I don't think it's very common [no] but nonetheless I have seen it personally. And we nearly lost somebody, not on a trial but just you know and had to be ventilated and two weeks on the ventilator. And the intensive care people are saying this is cancer, we should write it off, we should stop the ventilation because this is obviously cancer. And I said no it's not it could quite possibly be the drug and indeed it was the drug. And two weeks on the ventilator she cleared and came off. [wow, that's] So it's, you know, these things are in a way matters of life and death, they can be. **(attributions can be as serious as life and death)** Now, you know, we're told the incidence is 1 to 2%, maybe 4% in the western the world and 1% in the orient. And you know, I'm not pointing fingers but it is something that occurs at a low frequency that might be expected in the population anyway. And I think it's just interesting if you're looking at a case history to go back and say well what is the history of this attribution, when did it become, when do people really know about it? Is it possible that people under attributed it earlier on? You know, were there accusations that there was over attribution? You know, because, I'm not saying this company is an ethical company but they're, but is it possible that some company with some drug might pressurize people not to make the attribution? [sure] You know, what do you do under these circumstances, what is your responsibility? And I think a lot of things can happen under the, under the banner of uncertainty. You know, you can be forced to under, I think that uncertainty is at the heart of this, its at the heart of this. And I don't think it's a matter of honesty or dis, I think it's uncertainty and how do people cope with uncertainty? And I think that this actually is the measure of whether enterprises succeed or fail. You know, it's how they deal with uncertainty. So I think for example one of the differences between successful businessmen and unsuccessful people in business is that the unsuccessful people don't know how to deal with uncertainty. Um, because life is full of uncertainty and you know, it's possible to be panicked

into, into making a wrong decision. On the other hand it's also possible to be paralyzed into not making any decision at all. [yeah] So when you see these kind of little human dramas played out in this situation as well because, but I think it's a mistake to not allow the physician to be uncertain when he or she is genuinely uncertain. But what I don't see is like, you know, a highly refined scale about uncertainty. Like if you say okay, you're uncertain. I don't see a scale that then says well quantitate your uncertainty and do you think, how is uncertain, how certain are you that this, or what do you think is the probability in percentage terms that this drug caused this side effect? And I've never seen that ever. So if you say for example, there's a category of possibly, one of the things that you might consider is once you click, once you tick possibly due to this then give me your, try and put a quantity on your, on your sense that this has actually caused this. Is it 30%, is it 40%, is it 50, 60, 70%? And that might be quite interesting to go through as an exercise. To actually allow people to be uncertain and then make them quantitate what they think the likelihood is that it actually did that it actually did cause.

M: Well actually, that's quite interesting, can I just ask you to, I just want to describe a scenario to you and we can just sort of walk through it. So let's say for example you have a, a you have a female patient who has been diagnosed with metastatic breast cancer and um, she's just reported and she's in a Phase I clinical trial with an investigational trial and she's just experienced a pulmonary embolism. How would you assign causality to the study drug if you knew that there was a 75% chance that it was due to the study drug and a 25% chance it was due to other factors, say um...

S22: Well I would say it's probably [probably] probably. Yeah, I'd think you'd have to, if probably was an option [yeah].

M: So the scale would be certainly, probably, possibly or unlikely.

S22: Then I would say that it was probably due. But I'm not sure that I would know necessarily that the underlying, that it was 25/75 [yeah, so you would never know those percentages] I would never know those percentages. Unless I, unless somebody could tell me what is the risk of people on chemotherapy with, not chemotherapy, people with metastatic breast cancer, getting a pulmonary embolism off of chemotherapy. Because I presume she's not on chemotherapy, she's just on the new drug. So the question is what is the likelihood that this would have occurred anyway had she not had the drug? And it comes back, it comes back to our predictions to, and the answer is we don't know. So if for example, this knowledge was available to the physician when he was asked to make the attribution [right] that the incidence of pulmonary embolism, the woman on, with metastatic breast cancer, independent of treatment is you know 16% lifetime, you know during, from metastasis to death. There is a 16% incidence which I would say might be quite accurate, I don't know but it's probably around that order, maybe even higher. Um, so how does that help you? Well I think it does help you to a certain extent because you know it's not 80%. If it was 80% then you might be inclined to say well it's probably not due to the study drug and therefore I'm inclined not to stop the study drug. But if it's say 10% you'd say well I'm inclined to believe that it might be due to the study drug, um, and therefore I might be inclined to do something about it. Now in this case probably what you would do is put the patient on anti-coagulation and carry on with the study drug. It's probably what you would do, just like you would do with conventional chemotherapy. The real, the really difficult issue is where you would have a situation where you would have to stop the study drug or reduce the dose of the study drug. There I think it becomes particularly difficult and particularly important that the correct decision is made. If you're simply going to say well you can treat this with a bit of Imodium or some heparin or something it doesn't really matter. But where you're forced to interfere with the conduct of the study and the administration of the new drug that's where it becomes acutely important to do the right thing. **(uses the term forced again)** And that's where I suspect that people need help. So one of the things you might want to think about is maybe

you shouldn't let the physician by himself decide or at least have total ah, I mean I think the physician is ultimately responsible at the end of the day. But maybe there ought to be some centralized mechanism whereby some brain, artificial or real helps the physician make a decision, rather than just stop the drug or, you know, arbitrarily do something. One of the things that does concern me that I didn't tell you about before is where junior physicians particularly seeing patients in a clinic on trial will just say oh my goodness stop the drug you know, just do the wrong thing out of, sometimes out of fear, something bad has happened. You can imagine, you know, [it could be scary for someone brand new] yeah, because they see two weeks ago somebody started a new drug, now you know, the patient's skin is falling off. You know you get scared, what am I going to do. The safe thing to do is to stop you know. I mean this happened to me, again a couple of weeks ago, some patient came in with some really weird rash, weird rash and it wasn't like trivial, it was like you know, open oozing areas, this kind of thing. And the question was what, what could possibly be doing this you know. [right] And they were on an experimental drug at the time and we had to get a dermatology opinion and even a biopsy to try and sort out what was going on you know. And we did in fact stop the drug because I had not seen this before, it looked potentially quite serious. So you know, I think under those circumstances I think in a way you had little choice. But you can imagine there were many borderline situations where you know. And I think, I think if there were some central and I think the Internet can enable this, if there were some enabling technology where the principal investigator of the study could make a decision together with the treating physician rather than just some junior person stopping the drug or mistakenly carrying it on. So that also, that also worries me, the way decisions are made with respect to stopping or starting or reducing the dose of the experimental drug. **(worried about the authenticity of certain attributions)** That inexperienced people in a bind, in a clinic, in a busy clinic feel forced to make a decision. Whereas we now live in an age you know, with the Internet that you know some kind of advice [yeah] that you know was semi-quantitative or at

least more insightful. That this responsibility might be shared and a more rational decision could be made.

M: That's, yeah, I think there's a lot of work that can be done to improve a lot of the processes for sure. [yeah] That's a good idea. You mentioned that uncertainty is sort of at the heart of this and that the unsuccessful ones don't really know how to deal with ah, with the uncertain um. The companies that are unsuccessful are the ones that don't know how to deal with that uncertainty and I guess sometimes that can lead to pressures. Have you ever, you know, what sort of external influences or pressures have you ever felt?

S22: Well yeah, I would say, you know, just without

M: Not necessarily from companies either, just any sort of third parties.

S22: Yeah, I think that companies, consisting of human, they're all human beings you know and they tend to, they tend to drink their own kool-aid you know. Um, they sort of believe their own propaganda in a way and they're very nervous about putting reports out with respect to side effects. So, there's no doubt you know, I've seen situations where, you know, people writing up papers or abstracts have been monitored quite closely by the companies with respect to what they say about side effects.

M: So if the PI of the trial is writing up the, the study results?

S22: Yeah, I have, especially interim reports more so than with final reports, certainly interim reports. I have seen situations where some pressure, let's say that the pharmaceutical company maybe had a different viewpoint about what was said, you know without being specific I've certainly seen that. I think most people have, most people that deal with pharmaceutical companies realize that they're obviously coming from a certain angle. And that they may have a different

interpretation, sometimes, I think sometimes they're right. I think, I'm not saying they're always wrong but certainly they have a viewpoint [sure] which they express you know. [laughter]

M: Any other pressures when you assign causality or from third parties?

S22: I think you know, if a patient is sick in a way that taxes the resources of the cancer center and the hospital, I think you know, there's certainly pressure not to carry this on beyond what's reasonable. And you know, that's, that's understandable and inevitable.

M: So that would be sort of from the cancer center?

S22: Yeah. You know, let's say a drug causes profound anemia and somebody has to be transfused over and over and over again. Is this, you have to think about, you know, no man is an island, no person has got an exclusive claim on the resources of society ad infinitum. So I think we have to make judgments about whether they've crossed some kind of threshold of reasonability. [yeah, yeah] You know, and I think you know, some of the, some of the new stuff, some of the new drugs that we test inevitably are going to make some people seriously ill, even if it's a small minority of people who are seriously ill. They're going to be in intensive care units, they're going to extract, they're going to use a lot of resources. So I think doing clinical trials is actually a resource intense occupation that can really only be afforded in quite wealthy countries actually. [definitely] You know, to do it properly and to look after people on the downside. I was just watching TV last night about these 6 people in the UK [oh right] I don't know if you're familiar with that story. [yeah, just this past March] Yeah, I don't know exactly what they've got and what went wrong but it didn't look good from the report on the BBC. Life long side effects you know, eradication of their immune system you know [previously perfectly healthy] previously perfectly well. [healthy

people yeah] So, how come, how come 6 of them, you know, why wasn't it picked up on the first one? Was there an under attribution problem?

M: I think in that case what happened was they started infusing one and then half an hour later they started infusing the next one and then the next one and they didn't leave enough time.

S22: So there's a thought you see about how these, about how it's spaced out. So that once something happens, should a mechanism kick in to permit sufficient time to evaluate [definitely] before they treat the next section?

M: I'm not sure how that trial passed through you know to be performed in that manner.

S22: Well yeah, again, I don't want to point fingers because all of us have to learn as we kind of, as we go along. But I think it's just important that we do learn [yeah from our mistakes] from our mistakes. [definitely] I think that's the least you owe people is to learn from mistakes. [definitely]

M: Well I don't want to keep you anymore, this has been wonderful. I really, really appreciate the time that you spent with me.

Subject 23

M: I will just explain a little bit about what it is that we're doing. Even the most experienced physicians find signing causality to adverse events challenging. And many groups such as industry sponsors, clinical trial cooperative groups and research ethic boards, they all expect prompt and sensible causality assessments. But I'm sure as you know it's not always very straightforward and if done poorly there are implications to that. So our thought was that we would like to develop a tool to help clinicians more efficiently and reliably assign causality to adverse events that occur specifically in the early phase oncology clinical trials setting. And we feel that by better understanding your needs as a clinician, we

can make this tool more relevant to you, the end user. So, do you have any questions about that? [No] Sounds pretty good? [sounds like a wonderful idea] Okay great. So first I'd just like to get a better understanding of the, the clinical reasoning that you use when you are attributing causality. And this is going to sort of help to inform the development of the tool. So let's say one of your early clinical trial patients, let's say they are an early phase oncology clinical trial patient, reports experiencing a serious adverse event. Can you just walk me through your thought process?

S23: Well the first thing is if it's a drug we have used fairly regularly we would kind of relate it back to whether or not we had seen it previously, or ah, in the letter of information and consent, if it's listed as a likely side effect of the drug. Other than that, especially for serious adverse events, we get all the information we can get from the hospital where the patient has been admitted and go to the, fill in the form as much as we can and then basically sit with the physician.

M: Sorry what do you do with the physician?

S23: Sit with them and, and review it with them.

M: Okay, so you review it with the physician, yeah.

S23: Because you can mess up a lot of you're, when you're messing with Phase I causality, it can make quite a difference. I mean 20 years from now they go back you know, the drug has been shelved because of it, so it can have a lot of repercussions. [right]

M: Have you ever experienced that where a drug has just not made it past the Phase I stage or?

S23: Um, occasionally with some of the IND drugs that we use yeah.

M: Can you give me an example or?

S23: There was one we used in melanoma a few years ago and then we used CCI779 and in the site we were using it in, it was not effective.

M: What site was that? [Melanoma] Okay. So I guess it was halted because of lack of efficacy more so.

S23: Well more so but there was a lot of problems with some of the toxicities as well, all the patients were having serious adverse events. But they were also very ill patients and it's very hard to separate that out at times.

M: Okay, so you look at whether the event has been seen previously, do you mean in previous trials that you've done?

S23: Well we try not to cross trials because sites can make such a difference too. So we try to stay [disease sites] yes, stick to the same sites so if we're doing a GI trial in colon and we see a side effect we will look back on the other patients that have been on that study. And also at the letter of information and consent, the IB basically, and ah, from there go to the physician. Usually if there's a lot of doubt we go with possible and go back and forth with the company.

M: What do you mean go back and forth with the company?

S23: Well we'll fax it off and they'll say, you know, they'll come back and say why is this a possible relation? and the physician will say the reasons he thinks that it could be because he doesn't know that it isn't so he will do a possible. And occasionally we change that either to probable or unlikely but normally we stand pretty firm with what our initial gut is. **(goes with their intuition)**

M: So it's not uncommon then for the company to ask you to justify your causality assessment. [mmm hmm]

M: And so you mentioned that some of the resources you refer to is the IB, the consent, form. Any other recourses that you use?

S23: Those are the primary ones I use and then to the physician after that. I guess occasionally with drugs that we use a lot and there's something odd I'll go online and see you can find any reference that but we certainly don't base it on that because that's usually on an individual case basis.

M: What sort of tools do you use to help you when you are assigning causality do you have any? You mentioned this PAR form.

S23: We've got this PAR form. [okay let's talk about your PAR form] Okay. We just developed this lately and it's based on the version 3.0. And what we've done is we've gone through the toxicities, the most common toxicities we see across the board because we use it in every site. So for nausea we've kind of gone through and thought well almost every, it's mostly for chemotherapeutic agents. Almost every drug causes some form of nausea or vomiting or something like that. And so if we start with this as a baseline and we have a good feel for the patient, it's a lot simpler obviously to give the relationship to the drugs. The problem we're running into with this form right now is first of all, the physicians, because it's new, they're not being very helpful in clinic, because obviously they're used to their old ways. Quick glance at the PAR, see what's going on and with the patient and back out again. And the other thing is because we're starting this mid-stream for a lot of the patients it's very difficult to say in clinic alright well do we call it a 3 or a 4, what have we been calling it? Because we don't obviously have the CRFs with us right. So a lot of them have been left blank right now, so I don't know how to fix that. [right]

M: So ideally you would want to start this form when you're [at the initial stage] assessing them at their initial visit. [mmm hmm, mmm hmm] And um, now is this, is this based on, was this developed in house? [mmm hmm] yeah. And is this using the common toxicity criteria grading [yeah, yeah] for the severity. And this causality scale, who's scale is that?

S23: That's basically just, I don't even know where that comes from but that's basically the one that all the CRFs use so that's why we pull it out. I'm sure there's a reference for it someplace.

M: Because I have seen different causality scales used and just wondering if this is sort of the NCIC scale or the.

S23: I guess if we had to go back it would probably be NCIC that we started with. [yeah, yeah]

M: Okay, so this looks great. So these are just sort of the most common ones that you're likely to see [mmm hmm]. And then what about if there's one that are less common, what do you do?

S23: We have a section at the back.

M: Okay, here we go, oh, so you've just left some blank so they can fill it in [and some white space so that they can clarify those]. And so then each, one of these is done for each visit [yeah] okay, great. Will I be able to keep this? [mmm hmm] yeah, that's great. Very, very good, because I think that it would be definitely useful to the CRAs at the JCC. I'm not sure what sort of things they're using right now but I haven't seen anything this good before.

S23: Windsor has one as well [do they] but they've got a lot more, not quite as much blank space on it so it was very difficult to follow along. And I think they're a

smaller centre so they have more time with the physicians and I think that was reflected on the form as well [yeah, yeah, okay, good, excellent, thanks] **(larger centers have less time with physicians)**

M: So that's one of the tools that you use, are there any other tools that you use when you're assigning causality?

S23: Um, really there's not a lot out there so we try to stay very specific for the protocol with the IB, the letter of information, past experience with those types of patients. [yeah]

M: What do you think would help make assigning causality easier?

S23: Well that's a very good question but I don't really have an answer because every drug of course is different. And you're going to run into a whole slew, especially for Phase I's of things that you don't know, don't expect. [yeah]

M: What would you say are some of the problems or challenges with assigning causality?

S23: Time, the physician's time. **(time constraints, initial reaction)**

M: The physicians don't have enough time [mmm hmm] they're too busy?

S23: Oh they're clinics are crazy. Dr. xxx when he was running in he was just finishing up a morning clinic that was supposed to end way before noon and we never do, we go through lunch every week. [really] And that's how all the physicians work around here anymore. [yeah] **(everyone is overworked)**

M: So they just don't have enough time [mmm hmm] to properly assign causality?

S23: Not in clinic, a lot of the times it's retrospectively. Obviously if there is something that's greater than a grade 2 we have to stop and review because we obviously have to do dose reductions etc. [okay]

M: Any other problems or challenges that you found with assigning causality?

S23: Um, well I guess not really because we do have really, if you go back to the IB and it's not there and it's something really unusual, it's the physicians discretion at that point so. I think we rely on the physicians ultimately and their tools and their knowledge of it. [okay]

M: Do you have any concerns about how physicians assign causality?

S23: Not usually no, because usually they talk it out you know, like this is what you said in your note and this is what's happened to the patient, so we just kind of talk it out so not usually. Our physicians, well most of them have been here a long time so they're pretty experienced, well Dr. xxx is new but she's got a lot of Phase I's in her past as well.

M: Now are there any other external pressures or influences that you felt when ah, when assigning causality?

S23: Um, they're there but we basically ignore them [okay, and what are they?], because ultimately. Well it's the companies they want to get their drugs to market and sometimes you get a little pressure from them you know? [to do what?] Well to just to confirm yes this is related particularly if it's nasty, nasty stuff. There's a couple of companies out there that don't think twice about picking up the phone, you know, asking you to review with the physician, that's fine we'll review it but ultimately we're not here for the trial. Well we're here for the trials, but we're here for the patients and so we're not going to cause them any harm if we can help it. **(patients are the main priority)**

M: Yeah, that's the right attitude I think.

M: What I'd like to ask you to do now, if you wouldn't mind is read over these 10 questions and cross out any that you do not feel are relevant to assessing causality in the Phase I clinical trial setting.

S23: Did the adverse event appear after the suspected drug was administered? A lot of companies still make you do a serious adverse event even if the drug hasn't been administered. [really?] Yeah, a patient walks out the door and falls and breaks their leg it's a serious adverse event because they've consented to the study. [oh my gosh] It happens very regularly. [and they haven't even received the first dose yet] Exactly. Usually it's the smaller companies that are trying to make their mark I think and they're being overly cautious. [long pause] Half of it.

M: Oh great, now if you could just rank them, you probably already read it. If you could just rank them from most important to least important [mmm hmm], so 10 is most important. [okay]

M: Great, thanks. So I see that you crossed out number 6, and oh [just part of that one] just part of number 8.

S23: Just we would never increase the dose if there was a serious adverse event [okay, no, but you would decrease it] potentially decrease and continue yeah.

M: And then number 10 was most important, was the drug detected in the blood in concentrations known to be toxic.

S23: We do a lot of PK's in Phase Is.

M: And then next was, was the adverse event confirmed by any objective evidence? [mmm hmm] What did you understand that to be?

S23: A lot of them actually, a lot of them could be clumped together rather than [yeah].

M: So which ones would you kind of clump together?

S23: Well not so much those, any objective evidence on physical exam or, or blood results that came back. Or heaven help us if we actually had a CT right when something was going on. [yeah, okay, something like that alright]

M: And then least important was did the adverse event appear after the suspected drug was administered, why did you?

S23: Oh, I'm sorry, I read that wrong, sorry, no that should be up there a little higher than a 1 [oh, okay] well maybe a 7 and a half. [okay good]

M: So then are there alternative causes other than that drug that could have on their own caused the reaction, that was what you marked as lowest [mmm hmm] why was that?

S23: Well, yes because something else may have caused it but we don't know that this particular drug didn't cause it as well, especially if it's in early Phase I. And that's probably where we would go with the possible relationship as opposed to probable or anything else. [okay]

M: So what did you think of this overall as a tool, do you think something like this would be helpful?

S23: Well it makes you stop and think, yeah it does, especially to try and rate them, it's very difficult. It would depend definitely on ah, well the patient to some extent, the physician you are working with.

M: Do you think something like this, it would be feasible to complete something like this at the time when you're assigning causality?

S23: I think if we made part of our, especially for serious adverse events, part of the whole process that would make it a little easier.

M: So what do you mean when you say make it part of the?

S23: Well when we start the serious adverse event form, the physician, this would be part of his responsibility to review this with us. [okay]

M: So you usually fill out the SAE form with the physician there?

S23: Usually do most of it and then go to him at that point [okay] all the background stuff and con meds and . [yeah]

M: So this would be something useful to take with you when you go to the physician [mmm hmm] and say let's just work through this and do it together.

S23: Yeah, on an individual basis you know, it's a lot easier than just going, you know, trying to rate that. [yeah, yeah, okay]

M: What do you think, are there any other criteria for a tool that you think would be important, that you think it should or shouldn't be or what it should or shouldn't look like.

S23: Um, I think the simplest is always the best, everybody is always in a hurry, so something like a little tick box or check list, minimal writing, minimal instructions. **(time constraints don't allow room for exaggerated tool)**

M: What about if it was on the computer, sort of computer-based would that work in your environment?

S23: It would work for me, it wouldn't work for all our physicians [no] no, they, some of them just don't use the computer [they don't use the computer] not very often. [okay] I work with two physicians that, that don't. [okay, great]

M: Now lastly I would just like to ask you a little bit about your education [mmm hmm] that you've received, specifically to do with how to assign causality. So can you tell me about any education that you've received with respect to you know, how to assign causality to adverse events?

S23: Minimal at best [okay] basically on-the-job training. I think all the CRAs we basically self-train or train each other as we go. So as new people come on and basically if I'm training somebody I always tell them the investigator's brochure and the letter of information. Usually go to the letter of information first, and the investigator's brochure and if there are any questions straight to the physician. [okay, right]

M: Do you think some more education around this might be useful?

S23: Oh, definitely, but I've never seen anything. [no]

M: What, what do you think would be good in terms of education in this, you know, can you think of what?

S23: Well it depends how you go about it I suppose, I don't know how you would actually do it. I would think in classroom in small groups would be ideal because then you get a number of CRAs together and you get chatting and you learn more there then actually from any classes. Do you know if people have developed tools that they are using?

M: Um, I don't know of any at this point, but yeah we're thinking especially for the CRAs this would be really useful. You know, just to try to, maybe even just going through some case studies [mmm hmm] or you know, that kind of thing. Whether it would be sort of in a small group setting or whether it would be an instructional CD Rom or something I don't know. But yeah, we're thinking we'd like to develop something along those lines.

S23: Even a CD Rom would be excellent because you could stay on site and do it amongst yourselves with the CRAs. It's amazing, even when we were developing the toxicity form, of how many people, you think you know, everybody is doing the same but how, how little variances go over the years. And some of it would not, would not hold up. **(subjective)**

M: How, can you give me an example of how some people were doing things differently?

S23: Well it's just how they were assessing the patients as well, the PAR is built on this is the patient's norm so it's a variance from the norm. People were actually grading constipation as a grade 2 and in actual fact that was a normal for the patient so they didn't actually go up in grades. [oh okay] So a bit more education and you just kind of I think when you don't revise things enough people kind of fall by the wayside. **(education could aid in limiting individual variation)**

M: Just having those continual reminders about

S23: I would think it would be the same with something like this.

M: Yeah, yeah, okay, great. Um, let me just check here, I think that's pretty much all the questions that I have. Do you have any more questions for me?

S23: Not really. [no] But if you develop this I certainly would be interested in it.

M: In piloting it? [mmm hmm] Yeah, well what we would like to do is yeah, develop some sort of a tool and then we want to try and test it out in a clinical trial setting. It may, it may just be tested out at the JCC for now but um certainly what we're going to do is once we've interviewed all the people that we intend to interview we're going to summarize and put it into sort of an executive summary and send it out to all of the participants. So we'll let you know what comes out of these and stay tuned for the tool.

S23: Are you going across Ontario to all the centers or?

M: Well I've actually been out to the BC Cancer Agency, to here to this site, to the Hamilton, obviously, and then in a couple of weeks I'm going to be going to Ottawa. We tried to go to PMH but the ethics was just a nightmare so it wasn't, it wasn't coming together for PMH and I've been out to Kingston as well. [the larger sites] Yeah, the larger cancer centers.

S23: Kitchener or Windsor might be an idea because they're small they might handle things a little differently, may have a little more feedback.

M: Okay, great well thank you [you're welcome] I appreciate that.

Subject 24

M: I will just briefly go over what it is that we're doing. As I mentioned, the researchers that I'm working with we're, we're interested in how causality is

assigned to adverse events that occur during clinical trials. In the hopes of potentially developing a tool that will make things a little bit easier for, for people who have to assign causality. [sure] You know, even the most experienced clinicians find assigning causality challenging. But unfortunately many groups such as industry sponsors, research ethics boards, clinical trial cooperative groups, they all expect prompt and sensible causality assessments. [mmm hmm] But I'm sure as you know it's not always that easy and if done poorly there are implications. So as I said we're interested in developing a tool. And we done about, well I've done over 20 interviews now [okay]. And I've been told initially the CRA tends to assign causality. Can you give me an example of a time where you've had to assign causality or make that decision? Or do you even agree with that statement?

S24: Um, I'm not so sure about that.

M: No, not even initially?

S24: No, no, usually we just read through the progress notes, or find out from the clinician, clinician themselves.

M: Oh, okay. So I mean every centre seems to do it a little bit differently. [mmm hmm] How does it work here in your centre? Can you tell me about an SAE that you've had that has occurred recently and walk me through how causality was assigned?

S24: Recent SAE, um, I actually don't get a whole lot of them in my particular trial because they are Phase III prostate patients and they usually don't die off too quickly. [that's good] We did have a case fairly recently where the patient died suddenly at home in his sleep. The problem with causality with that was that there was no autopsy done. [right] So there's just a lot of guessing and there really wasn't one assigned for that. [so um,] Prior to that, we had a lady who was

admitted to hospital with ah, severe cystitis a result of her bladder cancer. [right]
But again, that was just going through the progress notes, the ah, and discussing
with the principal investigator and coming up with the causality to assign to it.

M: Okay, so you sort of work together as a team [that's right] to decide how to
assign causality. [yeah, yeah] Can you think of anything that would have helped
you in making that decision?

S24: Nothing comes to mind. Um, [can you walk me] since I'm really not the
person who actually sees the patient to and diagnose the patient, I'm really on
the outside of that, so there's really nothing I can do. [okay, okay]

M: So when you, your patient who experienced the severe cystitis and she was
admitted to hospital [mmm hmm] how did you become aware of that serious
adverse event? [um] Was it at her next visit that she told you about it?

S24: No, actually just kind of by accident really, just going through trying to figure
out when she was supposed to come back, they're supposed to come back at
pre-determined times and it just happened to pop up that she was actually
admitted to the hospital. [oh okay]

M: So she missed her next appointment or?

S24: No, no, we just ah, soon after they're seen we know when they're supposed
to come up, um, because we have these flow sheets and it says okay, they're
supposed to be seen on this particular day so that's when it's usually written into
the notes we know they're scheduled. Um, so she was coming, she was due in a
few days, so I just sort of checked to make sure that she was still coming in for
this one and I just happened to notice she was admitted. [mmm hmm, so she
was] We used to get lists of all the patients who were admitted to the hospital but
they stopped doing that about a year or so ago so it is just hit and miss now.

[okay, I see] **(must be very difficult not being notified if you're patient is admitted to the hospital)**

M: So this comes up on your computer screen and alerts you that she's been admitted to the hospital [that's right] and then you have to start the process of completing the SAE form is that right? [that's right]. And so then you try to collect all of that data and

S24: Go over there and go through the patient's notes and [so luckily she was admitted to this hospital] yes, yeah. Um, and then just read through the notes and discuss it with the primary care giver and see what's going on. And we sort of follow her for at least a couple of days before we make any definitive diagnosis or what is going to happen with her.

M: So in that case, how did you assign causality?

S24: um really it was just in the progress notes that she had developed severe cystitis and she was started on antibiotics. [okay]

M: And was that felt to be related to the study drug?

S24: It would have been related to the radiation she had received yes, she was receiving a combination of radiation and chemotherapy for her bladder cancer. [okay]

M: So you guys determined that it was likely due to the radiation therapy.

S24: That's right.

M: So how did you come to that, how did you come to that decision? What were some of the factors that you were looking at when you were thinking what was sort of ?

S24: Um really I didn't, I just read it off the notes.

M: Oh I see, so in the notes it actually said [yes] that they felt that it was probably due to the radiation [that's right], okay I see, good. So that one seems to be a fairly straightforward SAE [yes] where, you know, the investigators felt it was clearly related to the radiation therapy. [that's right] Can you give me an example of a serious adverse event that was maybe a little less straightforward that you've had in the past?

S24: Not, really, they've been pretty straightforward. [yeah] My patients, they usually don't die of their prostate cancer, I'd say about 90% of my cases are prostate cancer. [yeah] It's usually from something else, a cardiac event which is usually pretty obvious, or they develop a secondary malignancy in the lungs or they have a new primary to the brain. So they're usually pretty straightforward.

M: So they're usually due to disease progression.

S24: Not necessarily progression of the prostate cancer but a new primary pops up somewhere.

M: Oh, a whole new primary okay.

S24: My studies haven't gone far enough along to see death from disease progression. [okay, yeah, yeah]

M: I have been really surprised actually to hear that CRA's haven't received very much training with regards to assigning causality. Can you maybe tell me a little bit more about that or would you agree with that statement?

S24: Yeah, um, yeah, obviously we haven't received any training for it but um, I'm not sure that we're the ones who are actually expected to come up with that determination.

M: Okay, so you don't see that as being a big problem.

S24: Not really no.

M: Do you think that would be helpful to you in your job or that's just?

S24: I guess, I guess it would depend on institute policy. I mean really we're supposed to discuss with the co-investigator and investigator and come up with the causality and it's usually them that come up with it as such. [okay]

M: Are there any resources that you use when you're assigning causality?

S24: Other than the scans that the patients have, the tests and the progress notes, that's pretty much it. [okay]

M: And, and just based on that information you're able to sort of determine whether it's related to the drug or not?

S24: Usually for the most part yeah.

M: What about tools, are they any sort of decision trees, or flow-charts or algorithms or anything like that you use?

S24: No, not that I'm aware of. [okay]

M: Are there any sort of general guidelines that you tend to follow when you're assigning causality, any sort of rules of thumb? [loud sound] Oh my gosh, there's some noise coming from the next room. [starting windows] Is there a computer class next door?

S24: No, they're probably just starting up the projector that they have over there. [okay, okay]

M: It's just the recorder is highly sensitive to sound so it will pick that up probably.

M: What I would like to do now is just ask you a little bit about what you feel are some of the problems or challenges with assigning causality? Have you ever encountered any?

S24: Particular problems with it? [yeah]

M: Is there anything that's kind of tough in assigning causality?

S24: Nothing in particular pops up, I mean I can see there are some areas that obviously are a little grey as to which way the assignment should go, whether it's definitely related or somewhat related. **(certainty is difficult to achieve)**

M: Okay, what makes that difficult?

S24: We just usually decide with past experience with the drug. I guess it might just be a question of, maybe there's just the history is a little vague or the tests weren't 100%. I can see those sorts of things popping up but I haven't actually experienced those sorts of things yet. [okay]

M: So you said that sometimes assigning causality is a little bit grey and I've actually heard that from quite a few other people that it is a bit of a subjective process. But can you explain to me a little bit more about what you mean when you say it's grey, I'm trying to get a better understanding of that.

S24: Um, just a question of how likely was the event related to the study drug. Um, it may be a little ambiguous in terms of the results of the tests that the patient has had, they may not be quite definitive.

M: Okay, can you give me an example of a test that wasn't definitive or?

S24: Um, nothing that's related to an SAE that I've had [okay] but I mean some of the scans just don't pick up things as well as others, you have to probe a little bit deeper sometimes, they just don't.

M: Yeah, so just the type of scan or?

S24: Yeah, we question whether it's a CT or an MRI or something like that. Some of them are more sensitive than others for picking up certain processes. [okay]

M: And so you know, you have these test results but you can't rely on them 100% [um] is that what you're saying?

S24: Yeah, um, in terms of what shows up or what the physician who is actually looking at the scan and dictated the note comes up with, sometimes they're kind of short with their dictations and some of them are quite extensive in detail. It varies from physician to physician. [right, okay]

M: You mentioned that sometimes the history is sort of vague, like the patient's oral history that they're giving you, is that what you mean?

S24: Um, not my, not the one that I would take, say one of the physicians maybe, some physicians are quite short in the dictations and so may not catch everything. [okay] **(time constraints)**

M: So the physician meets with the patient [mmm hmm] and afterwards they come out and they dictate what sort of went on. [mmm hmm] And often times it's not extremely detailed, is that what you're saying?

S24: I wouldn't say it's often, but yeah, sometimes.

M: Sometimes it's not really detailed. [yeah] Okay, and do you know why that could be or?

S24: Lack of time probably. [just time pressures, yeah, okay that would seem reasonable] **(time pressures seem to be a major trend)**

M: So those sort of things all combine to make it difficult to determine how likely the event was [mmm hmm] related to the drug? [yeah]

M: What are your concerns about how clinicians currently assign causality?

S24: Can't say that I've actually had any myself [no] no real concerns for it [no] no. [okay]

M: Some people have said that maybe it's done a little too quickly or it's, it's not really well thought out. Would you tend to agree with that?

S24: No, not in my experience no. [okay]

M: What external pressures or influences from third parties have you felt when ah, when assigning causality, have you felt any?

S24: No, not in my studies, very little um, pressure from any of the drug companies that we deal with. [okay] But then again mine are more local studies.

M: Okay, that are initiated by local PI's?

S24: Local PI's yeah, they may get some funding from some of the drug companies but not like some of the other CRAs that work here where they deal primarily with sponsors and drug companies. [okay] So they would probably have more pressures. **(drug companies may place added pressure on causality attribution)**

M: So then from your perspective what would make assigning causality easier? Can you think of anything that might make the process easier?

S24: Um, if there were any courses or literature on how to define it or come up with better ways then yeah, I would certainly be willing to take them. [mmm hmm] But I haven't heard anything about that.

M: So courses or literature on how, on just sort of how to do it or?

S24: Yeah, how to do it or guidelines, because I don't think there's anything really written in stone as to how to assign it or how, the process to actually do it, I mean the physicians usually just sort of come up with something. **(lack of standardized tool)**

M: Is it a kind of a mystery to you how they determine the causality or does it seem fairly, clear?

S24: No, it's usually fairly clear. [yeah] But then again I don't have the medical background that they do so.

M: Do they usually take the time to explain to you why they have assigned it a certain way? [it varies] It varies by physician? [yeah]

S24: Sometimes it's fairly clear-cut and it's kind of obvious and I don't ask, but other times I will ask, they're usually pretty good about it. [okay]

M: What I'd like to do now, is take a look at an algorithm that was developed by a researcher named Naranjo. And, ah, it's a series of 10 questions that might help in thinking about how to assign causality. I'm wondering if you could just give those a read over [sure] and cross out any that you feel are not relevant to the, specifically the Phase I, but if there are any that you feel, I know you mostly specialize in Phase III. [mmm hmm] Any that you don't feel are relevant, especially to the oncology clinical trial setting. [sure]

S24: Not sure how often number 6 happens [number 6] does the reaction reappear when a placebo was given? [okay] I don't have a lot of studies, or actually I have no studies in Phase I. [yeah]

M: Well feel free to cross it out. You know, this tool wasn't developed with oncology in mind [mmm hmm] so if you don't feel it's relevant.

S24: Yeah, I don't know that it actually would happen in practice here on a study.

M: Yeah, that's, many people have said that. [yeah] So is that the only one or were there others to cross out?

S24: No I think that's about it [okay] I can see that they might do this in a Phase I study but I don't have a lot of experience with that so. [okay]

M: Now I'm just wondering with the remaining questions.

S24: I think that would just be cruel [yeah to re-challenge with the placebo] yeah. So you want me to rank them in order of importance.

M: yeah, if you could just rank them, and 1 is least important and 10 is most important. So yeah just how important you feel those other factors are.

S24: So not an order as such, more of a rank. [yeah]

M: Great, okay, so number 9 you've ranked the lowest, did the patient have a similar reaction to the same or similar drugs in any previous exposure, why was that?

S24: Um, I wouldn't say that if they had a similar reaction it was indicative of having a problem this time around. [right] You know, I'd say they're all fairly important just that one was the lowest.

M: And now number 2 and 3 you ranked as highest. [mmm hmm] Did the adverse event appear after the suspected drug was administered and did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered? Why did you rank those the highest?

S24: They just seemed the most obvious without having a problem. Just the events started when they actually started the drug then more than likely they are having a problem.

M: So if there's a temporal relationship [mmm hmm] there's a timing [yeah] okay, if the timing makes sense yeah. So that's sort of, that would be the most important evidence [mmm hmm] to your causality assessment. [yeah] Okay, great. Now was there anything on here that you felt was missing or should have been there but wasn't?

S24: No, it's pretty complete.

M: What did you think of it as a tool, you know going through these series of questions would be useful for every SAE that you have or?

S24: Yeah, I would say so, but most of the time you're going through those in your head anyway [you're sort of thinking through it] maybe not all of those but yes. For the most part when you are going through, okay when did it happen, timing of events, that sort of thing yeah. [okay]

M: Alright, is there anything else that you think might be useful, sort of as opposed to this or what sort of, you know, if we are to develop a tool [mmm hmm] you know, what are the criteria, how should it look and what should it? What purpose should it serve, how would it fit into your daily routine?

S24: In terms of what layout or how it would look or?

M: Yeah, well I guess just more sort of, we want to make sure that this is something, you know, that you're going to find useful [mmm hmm] and want to use every day or every time you have an SAE. You know we don't want to create additional paperwork [yeah] or you know, that kind of thing, we want it to be useful. You know, maybe if it could pull other information in or, I don't know.

S24: What are you thinking of having this as a computer type thing or?

M: Yeah, we could, definitely.

S24: Pulling it from various sources or?

M: Yeah, it could potentially be an internet-based type tool or.

S24: That would probably be of most benefit. I guess what, if it could pull similar events from ah, that particular drug automatically.

M: Okay, sort of events that have happened [mmm hmm] in the past [mmm hmm, yeah].

S24: I don't know how we can tie that in with any other tests that have been performed as such. That would be quite daunting I would think.

M: Oh you mean like linking it to the patient's history? [yeah] Well maybe, [good luck with that] down the road.

S24: Specific lab tests that you could punch in or something like that. [mmm hmm]

M: Okay, great. Now what's the scale that you use when you're assigning causality?

S24: Since I don't really do it? [laughter]

M: On the SAE form there should be some sort of a scale.

S24: Yeah, there's usually, what is it ah, likely, unlikely, definite, not at all, there might be one more. [okay]

M: And do you prefer to have that, that scale or would you prefer a yes it's related to the drug or no it's not related to the drug.

S24: No, I think definitely the scale. **(leeway in scale measures is comforting)**

M: Why is that?

S24: I think sometimes it is a little ambiguous as to is it really caused by the study drug or procedure, it's nice, it would be nice if you could say definitely [yeah] but it's not always the case. [no]

M: Can you give me an example of a time when it was sort of ambiguous and you needed that scale?

S24: If it was, could be attributed to a number of different factors then yeah you really can't say whether it's definitive for whatever you've given.

M: So what would be some of the other factors?

S24: The patient's condition, if they were somewhat frail to begin with, if they already had a cardiac history and did the chemo drug induce that or was it just some event that was going to happen anyway? [right] There's a lot of things that come into play, it's not always a case where you can say yes. [right]

(confounding variables)

M: So is it the, so all of those factors kind of are what makes it grey [mmm hmm] what makes it ambiguous. [yeah]

S24: I mean if the patient didn't have any cardiac history or any neurological history then you could say, sure this is definitely attributed to, but this patient population is elderly and there is always something going on [yeah] at the same time. **(assumes comorbidities with their patients)**

M: Great, well I think those are all the questions that I have, do you have any other questions for me? [no] No, okay, well thanks very much for your time, I really appreciate it.

Subject 25

M: So basically I'm working with some researchers at the Hamilton Cancer Centre and they're very interested in how causality is assigned to adverse events during clinical trials, specifically oncology, or early Phase oncology clinical trials. [okay] And even the most experienced clinicians find assigning causality challenging. And um, many groups such as industry sponsors, clinical trial cooperative groups, they all expect prompt and sensible causality assessments. [mmm hmm] But I'm sure as you know, it's not always that straightforward and if it's done poorly it can have some large implications. [right] So our interest is in developing a tool to help in assigning causality more efficiently and reliably. But we feel that by better understanding your needs [mmm hmm] we can make this tool more relevant to you. [okay]. So do you have any questions then before we start? [um, no not at this point] Okay. Did you want to say anything about the way things work here or your role as a CRA?

S25: My role as a CRA? sure um, I guess step-by-step would be the physicians identify patients here that they think would be a candidate for a study. [yeah] And in turn they would contact us and together we would review for eligibility. Um, we sort of work together with the physician to enter patients on the trial. Once the patients are actually on the study we see them every cycle or every visit while they're on treatment and in follow-up. And we, we usually see them before the physician, we'd just go in and chat with the patient while they're waiting and sort of go over um, any sort of symptoms or adverse events that they have experienced. And then we would review with the physician at that visit and together talk about what's happening with the patient's after each cycle of treatment, even, well during follow-up too. And then together just

M: And then if there's been a serious adverse event [right] how, what happens in that case?

S25: So if there's a serious adverse event, depending on how we find out about it or when. Um, if we found out about it, if they were admitted to the hospital, usually the physicians would phone us, they usually find out and phone us. Or we would let them know if a family member contacts us or something. And then we report it um, the initial event, we would report that right away, what we know to have happened right away. And then as soon as we get any follow-up information or as soon as the patient is discharged from the hospital then we would complete the event.

M: So we've done a little over 20 interviews now [right] and um, what some have said at least initially anyway, a lot of time the CRA assigns the causality because there is that tight deadline of 24 hours. [right] Would you tend to agree with that?

S25: Definitely happens for sure, definitely, because we're doing that initial submission that we may. Often the physicians sign off the report, not always the initial, but if we, if we're with the physician, if we can talk to them at that time that we have to submit it then we would try to find out. But yeah, often we would go to whatever tools we have to try find out if it may possibly be related. **(do try to make use of the tools available to them)**

M: What are some of the resources you use then when assigning causality?

S25: Well definitely we would go to the protocol, the investigators brochure, um.

M: What are you looking for when you're looking in there, in the IB what are you going to look for?

S25: Um, looking for events that may have already happened in previous studies that they think may have possibly been related. We look at the consent form.

M: What are you looking for on the consent form?

S25: Any adverse events that might be listed, whether or not they think they're possibly, most of the companies now put whether there's a chance that it might be related or not, so we look through that as a tool. [okay]

M: And the protocol how does that help?

S25: Um, some, some of the study, or sorry the companies, not all of them mention, but do actually have tools right now where they would give some examples or sort of pointers I guess to help us out in, in assessing causality to the event. Things we could follow through like, I don't know how to, it's been awhile since I've had a tool like that. But it's very rare, I can think of one company that has it, even [someone comes in room], yeah, they just have a tool to help you, to guide you in whether or not the event might be related or not.

M: Do you remember the company?

S25: I think it's AstraZeneca that has a tool like that, it's been so long since I've done anything with them, I've only come across it once.

M: And what does the tool do?

S25: It's just sort of gives you pointers in, in different events and what to look for and what may possibly be related and not related. [mmm hmm] But the other protocols we would just look um, same thing like the consent, and what they think might be a possibly related event. Mostly the consent form has that information for us. [right] There's not a whole lot to go to. [yeah]

M: So what would sort of help you then in making that decision?

S25: Um, I think something similar to what that one company I was talking about has, I, I think for us we keep in our patient charts right now for example, um, all the dose modification rules for stopping the drug. If, if an event happened, um, so we sort of follow through with that, and that even lists what events to look for to do the dose modification or

M: Okay, so where are you getting those documents from?

S25: In the dose modification information.

M: And where does that come from?

S25: In the protocol, sorry [okay]. So we copy that information, we keep that right in the patient's chart. So if something was to happen, if they experience some event we can go right to that information. And um, usually the, the companies will list what they know to be the more common events so we can go right to those. If it's something that we know is expected, I mean the physicians with any chemotherapy know what's expected of our standard chemotherapies. So we could go to that for example and then it would give rule as to what to do with the drug. So I think in maybe that section of the protocol um, there could be some type of a tool, where they could list, it's already kind of listed like that, I'm just trying to think of a good way [what's already listed] what's some of the more common events [to expect] to watch for, to expect. **(list of common toxicities is not sufficient enough, need for something greater)**

M: With the new drug or with the standard chemo?

S25: With the new drug, sorry, the protocol drug. So I'm just trying to think of some kind of guidelines for us to follow, like what to look for. [mmm hmm, yeah that's good] Something to add to that section of the protocol, maybe that...

M: Yeah, so that would make assigning causality a little bit easier [yeah, yeah] if it was more readily available and clearly laid out. [right, yeah]

M: Are there any tools that you use to help you when assigning causality, like any sort of, I'm thinking more like a flow chart or a decision tree or some sort of algorithm?

S25: Just the, we photocopy, like I said the sheet we take right out of the protocol, we copy the dose modification information.

M: So that's the only decision-making tool.

S25: That's really our, that's really our tool that we use. [yeah] Other than the consent form where it lists all the different events to look for or to expect the possible side effects. [okay, good] Yeah, that's pretty much it.

M: Are there any sort of general guidelines that you tend to follow when you're, when you're assigning causality?

S25: Well definitely we don't make the ultimate decision so the physician will always make that ultimate decision. We have a um, when we see the patients in the clinic we do have a standard sheet we use, an assessment sheet and we um, on the back of the sheet it lists um, probably about 10 standard sort of events that patients would experience with chemotherapy. Things like nausea, vomiting, diarrhea and then we leave quite a few blank spaces so that when we assess the patients and they tell us what's happening during their cycles, we keep track of all that, we grade them, put the start and stop dates. And then we have a section for causality, so initially we may put the cause but then we always go to the physician and they'll review it and sign off on it. [okay, that sounds good] And I think for them, I don't want to speak for physicians, but the same thing, from knowing the protocol, reviewing the background of the drug we're using, going to

the meetings. They have an idea of what to expect from the drug, but again, there are always new things that are happening so. But ultimately it's always the physician that makes that final [right okay] decision. [okay, good]

M: What I'd like to do now is ask you to consider a scenario for me. [sure] So let's say you're treating a 65-year old female patient with a confirmed diagnosis of metastatic breast cancer [okay] in a Phase I clinical trial with a new investigational drug when she experiences a pulmonary embolism [okay] So obviously an SAE. How would you assign causality to the study drug if there was a 75% chance that it was due to the study drug and a 25% chance it was due to other factors?

S25: So probably related, all the companies have different [different scales] yeah different scales to use. So I'm saying probably but it depends on the scale they have.

M: Okay, so let's say I give you the scale of certain, probable, possible or unlikely.

S25: Probable [you would say probable] definitely.

M: Okay, why would you say probable.

S25: You said probable, sorry can you just read them again?

M: yeah, certain, [right] probable, possible or unlikely.

S25: Okay, I was going to say I didn't hear definite but that's certain. So probable because it's not 100% chance that it would be related [mmm hmm] but 80%, or 75% is a pretty good chance that's it's definitely. [mmm hmm 75 is pretty high] And then ultimately again I would let the physician make that decision but it

would depend, there's always a chance it could be a disease related event too.
[yeah]

M: Alright, now let's say there was a 50% chance the adverse event was due to the study drug and a 50% chance it was due to other factors. How would you assign it given the same scale again?

S25: So possible. [possible okay] It's the same scale you said right? [yeah, same scale] Okay.

M: And now let's say there was a 20% chance the adverse event was due to the study drug and an 80% chance it was due to other factors. How would you assign it then?

S25: So we have unlikely, possible, probable and certain, just the 4 [yeah] and it's 20%, I would probably still say possible [yeah] yeah, I'm kind of in a tossup there but yeah. **(goes with intuition)**

M: And what would be, what would be sort of your lower limit then to say that it was unlikely?

S25: Hmm, I would have to go with the physician's assessment, just if they really thought it was more disease related than something that was caused. I'd have to sort of read a little bit more into it to say it was unlikely, I'd have to have a little more information I guess. Because there's always that one chance, I know unlikely there's still that chance, but I guess until I had more information or spoke to the physician I would still say possible. [yeah] **(feels comfortable consulting with physician)**

M: And can you tell me, tell me a little bit about how you determine whether you should call it probable or possible, like how do you, how do you make that distinction, between probable and possible?

S25: Well again, like I said, I'd have to have more information to make that decision. But if it's something that is um, there's a big percentage of that event occurring with the study drug, for example, and this is something that the patient experienced. Depending again on the timing and when it happened to her and what disease, or what disease the patient had then I would definitely go with probable over possible. Unless it was something that was happening with this particular patient with her disease, you know, then I would definitely say probable. [yeah, if you know that it's] With a large percentage of patients on this particular study drug where this event is occurring, that's, me personally how I would base that. **(very subjective)** [yeah] It's hard though without more information, I know the initial sort of, I think, I guess it's better to go on the higher end of the scale because it's a study drug, you know, to be safe [yeah] until we have more information, when you're doing that initial causality. [yeah] You know, because it's a safety thing that you're sending out there so I guess that's the way I would go with it. [sounds good to me]

M: So you said if there was [It's hard to think about how you do all this] yeah, and so you said if there were a high number of patients on the trial that were experiencing that same event [right] then that would more likely be possible or [probable right] probable. And how, how do you know about that, how do you know if there's other patients?

S25: From other events, safety events that are coming to us from other sites, or the company, any of that sort of correspondence that's coming through to us. Or information from previous trials, it maybe something that's already known when we start the study. [in which case it would be in?] It would be in our consent form or protocol, that's right, something that we would already know starting. [yeah]

But again, for that initial for me, if, if, I wouldn't base it solely on um, she had the event and she's on a study drug so it's probable. I wouldn't base it solely on that because she's got a disease and I don't really know any information. So I would definitely go to my other sources first to make that [yeah, yeah] causality, before I just said oh yeah, it's probable, because she's on a study drug, I wouldn't do that. [no, no, no]

M: And this is just a very hypothetical scenario.

S25: Yeah, definitely I would um, yeah, that's how I would do it. [okay good] And of course if it's something that we thought was probable we would be in contact with the physicians to try and figure it out as well from their point of view [oh yeah, yeah] as a safety issue so. **(safety is a prominent concern)**

M: What would you say are some of the problems or challenges with assigning causality?

S25: Um, ah, well just that, that, it's always, you never know whether something, there could be that chance that you don't know whether something could be related if it's a new event if it's happening with our patients. Um, you know, getting in touch with the physicians here just to work as a team to try and figure it out. [is that] And as you said, it's the source, where to go to other than the consent or the protocol to know, you know, what we're looking for.

M: So sometimes you find it difficult to get information?

S25: Yeah, more detailed information I guess, other than what's in the consent form, having a list of expected events and maybe, some of them put in the percentages of what the patients have already experienced. So yeah, I guess that, just a more detailed sort of, um, like I was saying we go to the dose modification and it will list sort of what the expected toxicities are and the rules to

follow. **(lack of detail in IB)** So maybe to have some kind of I don't know, chart or information in that area to go to, to see what we're looking for and how they expect us to assign the causality. **(little known about the expectation of causality assessment)**

M: And you mentioned getting in touch with physicians sometimes is a challenge?

S25: Yeah, sometimes it is a bit challenging, but um, you know, with holidays and being away that's sometimes a challenge [yeah]. But for the most part I would have to say here our physicians are pretty ah, pretty available. And we always have sub-investigators if we really needed to, to get some information. So I wouldn't say that's a huge problem. [okay]

M: So the biggest problem then is the ah, just, you never know and it's sometimes difficult to get the detailed information about what's expected.

S25: Yeah, we can have, they do provide, companies do provide information as to what you know, what they've seen previously but there's always that unknown. So yeah, it would be nice to sort of have something, I don't know what kind of a tool you would make though with um, so many different studies and different drugs, how you would make something generic. Or if you're looking at study specific, I don't know what you're, what sort of tool you're.

M: Well that's the thing [that's a challenge] yeah, it is a challenge trying to decide um, I think ideally we would like to do something generic that would work over many different studies and many different therapeutic areas. But we might just need to focus in on you know, one particular [yeah] area for now. [yeah]

S25: Yeah, that's just it, all the different sites, there's always a different toxicity with all the different drugs and the different cancer sites so I'm not sure how you would...

M: But if they're using the same drug at different centers right [yeah] it should be...

S25: The same drug, but I'm just talking about all the different, because you're looking for some type of a generic tool for different Phase I studies is that what?

M: Yeah, yeah, just for Phase I studies yeah, for all Phase I studies. So you think that would be challenging why?

S25: Well I'm just wondering if for the different drugs how you would um, I'm just wondering how you plan, like what ideas you already have [yeah] to do this sort of tool.

M: Well actually why don't I just ah, I'll get you to do this exercise and this might help [yeah, sure] clarify a little bit about one way that we're thinking [okay] of doing it. So if you wouldn't mind just reading over these 10 questions. This is an algorithm that was developed by a researcher named Naranjo and he didn't develop it specifically with oncology in mind. But we're thinking maybe we could tailor it more to you know, the Phase I oncology clinical trial setting. [okay] So if you could just read through those questions and cross out any that you do not feel are relevant to the Phase I oncology clinical trial setting that would be good.

S25: And cross out any that are not relevant, previous conclusive reports [reading out loud]. So just put a check or an x or something.

M: Just cross out any that you don't feel are really relevant.

S25: Oh I see put the numbers up here.

M: Oh, so you're done [yeah] so with the rest of them if you could just rank them according to the level of importance in making the causality assessment. [long pause]

S25: Sorry, this is taking long.

M: That's okay, take your time, okay great. So um, was the adverse event confirmed by any objective evidence, you ranked that the lowest, as being least important, why was that?

S25: I just felt the other ones more important because with a Phase I, with the dose increasing I just felt that that and um, what else did I put here [whether it was detected in the blood] yeah, doing the blood and then whether or not the event would reoccur after the drug was administered. Or after it was administered to me might show you whether or not it was actually drug related or not because, what did I put for 8?, or whether or not it could have been another cause like disease or something else. I just felt that was more [those were more relevant] for a Phase I for me. [more important yeah]

M: What did you understand objective evidence to be? [um] How did you interpret that?

S25: Um, providing objective evidence, um, I guess, well I guess I could have rated that higher, like doing any other sort of, other testing, for me that's what I thought it meant [mmm hmm, yeah] scans or other blood work, things like that. I guess that to me, well yeah, I guess that could have been more up here with this one, if it was due to any other causes.

M: No, I don't want you to change

S25: No, no, it's hard to number them because there's so many of them [I know] for Phase I that we're allowed. But I guess the way I look at it and it's so hard to do this because in every situation is different. [yeah, yeah] So whether the patients, they may automatically do some test that's, that would prove right away that it was something else and then they may not re-administer the drug. So I guess I was looking at it with Phase I because you know, we're increasing the dose, that, and whether or not it happened before or after, during, to me would sort of prove if it was, it would give you some sort of idea about causality. It's a hard scale to [yeah] for me to do. [no, it's is, it's a tricky exercise, no question] Yeah because after you sort of read them, that's why I was having a hard time putting the numbers, you might switch your numbers around so. But this one for me would be sort of testing [yeah, okay] for example, if they were admitted for some event um, they might do some testing and they might rule out right away that it's [yeah] you know. If not then ...

M: They would rule out right away that it was due to the drug?

S25: If they could rule out right away that it was due to disease or another cause. But I guess that's why I put these as higher numbers for me for a Phase I, I guess, what was the other one here, ah, this one here I guess I should have put as a higher [number 3] did the reaction improve when the drug was discontinued or antagonist was administered. Between that one and did it happen, did it become severe when the dose was increased. I guess in a Phase I those would give you some kind of inclination if you already knew of an event that might be a probable or possible [right] event to look for.

M: Now I see you crossed out number 9, did the patient have a similar reaction to the same or similar drugs in any previous exposure? How come you crossed that one out?

S25: Um, I guess with the Phase I they wouldn't have had this drug before so. Typically they shouldn't have already received that drug if they're going on, that's why I crossed it out. [because usually patients] That's the way I interpreted it so [it's a brand new drug so they wouldn't have received it before] yeah, that's how I'm interpreting that one.

M: And then number 1 you crossed out, are there previous conclusive reports on this reaction. Why did you cross out that one?

S25: Yeah, I guess because it's Phase I and it's new and they're trying to find the different events for a Phase I [yeah] yeah. [okay, great]

M: Yeah, so that's sort of the idea of something that we're thinking about maybe developing. [yeah] What, what did you think?

S25: Yeah, it's ah, like the same, like you would make it the same idea you mean for different, I see so you're not going specifically to.

M: Yeah, this is very generic but maybe just ah,

S25: I think they're all good questions and I think they're definitely questions that we have in our mind already when we're trying to assess causality. [mmm hmm] Um, so it might be a good little reminder tool for us you know of what sort of questions to ask, definitely. **(feels reminders would be helpful)** Like I said, I think there are things that we already ask ourselves when we're [mmm hmm]

M: What would make it more useful? [this tool?] Yeah, or any tool?

S25: Hmm,

M: What about if it was something that was sort of Internet based and you know, sort of thinking big, we could really try to bring in some other information or you know.

S25: Yeah, well I mean, Internet is always a good tool, it's quick, you know, easy access tool for us so that, yeah it's hard [what do you]. I think the questions are good you know, good little reminders for us.

M: And if you were to go through and answer all these questions, do you think this could help you in assigning causality on that scale, causality scale?

S25: Definitely, yeah, I just have a hard time answering it because every situation for every patient is different. [right] But I think based on the patient situation, these would be easier to answer because then you could say yes or no. You know, that would definitely help out. It's hard to number them for me when I don't know what the situation is, what the event is.

M: So you would actually have to try out the scale and see how it would work.

S25: Yeah, I would have to try it, but I think for me personally I think it would be easier to do this um, with the actual event, knowing what the event is. [okay] But I do think it is a good scale. [yeah, so that's great]

M: Were there any questions that you felt were sort of missing that should be included on there that weren't?

S25: Ah, no, not that I can think of off the top of my head. [good]

M: And now lastly I just want to ask you if you have any concerns, what are your concerns about how clinicians assign causality? [Um, concerns] About how causality is being assigned right now.

S25: Do I have any concerns [some people have said] sorry, go ahead.

M: Well some people have said that they think it's done a little too quickly [too quickly] or maybe it's not done as thoroughly as it should be.

S25: Yes I guess, um, I was going to say something similar to that, that they might be making decisions quickly without really going to source, some sort of source or really knowing. **(make decision when based on time constraints)** I mean, I find here though, we're pretty good to go back, we may make that initial decision but then we're pretty good to go back and discuss. So I hate to say that they make sort of hasty decisions. I mean, they're educated with the patient's disease so I would hope that they go to all of their sources [mmm hmm]. But yeah, maybe initially they make that decision and then ah, don't, don't review everything later and make a change that might be necessary. The cause maybe already assessed and it maybe incorrect. Other than that though, I don't really have a major concern about that. [okay]

M: What external influences or pressures from third parties have you felt when assigning causality?

S25: Um, well I find the companies, well they don't always agree and then ah, [with your assessment?] with our assessments. And you see that often in safety reports that come through, it's tends to be always a possible or probable assessment when it really may not be necessary. But not a major pressure other than they want to know what the causality is you know, with that initial, if it's an SAE for example [yeah] they want to know that right away because they have to send that out to other sites. [yeah] So you know, that's the pressure there to sort of um, get that answer quickly. And because we don't want to make that ultimate decision they may be getting our assessment initially that might not be the correct one so I guess that would be a concern or a pressure for me [yeah] to get the

physicians ultimate decision on [right]. Because they want the information quickly right with an SAE so. [yes] **(pull and push between time and certainty)**

M: So you said that the companies they, you know, you send them in your causality assessment sometimes they don't always agree. [yes] Do they come back to you and ask you to change it?

S25: Ah, yeah, they could do that for sure, they might phone us, or during monitor visit they might um, sort of query it and ask questions about why we, thought it was related or not. And then give us their reasons why they think it should be different and want us to change it and we might not always want to. So there's, there's always that happens, usually they would speak with the physician, we'd have them speak directly with them so they would discuss their reasons for their assessment. But it does happen. [okay]

M: Any other pressures?

S25: No, not that I can think of. [okay, great]

M: Lastly, I would just like to talk to you about the education you've received with respect to assigning causality to adverse events. I was actually, I've been actually fairly surprised that a lot of people who I have spoken to have said that there really isn't much education out there [no there isn't] in terms of how to assign causality to adverse events. [no]

S25: No, I'm just trying to think of what would be an actual, you know, education that we've had. But other than when we go to the investigator meetings and we review the protocol they, they sort of have their own charts with their different assessment tools. Other than that we just

M: What sort of assessment tools?

S25: Well you know, your, your points there where it's either probable, definite, those sort of.

M: So they'll go over the causality assessment scale that they want you to use? [yeah]

S25: But other than that um, as far as education as to how to assess the causality [yeah] I would say that's really minimal to none. [yeah]

M: Do you think something like that would be useful?

S25: Sure, for sure. [yeah] I think for new CRAs or somebody who hasn't had any sort of training, definitely. It's kind of like on the job learn as you go really [yeah] I mean there really isn't any specific training to that. [yeah] It definitely would be a helpful thing for new people starting. **(feels education/training in causality assessment would be beneficial to new staff, no mention of current staff)**

M: What do you think would be the best way to deliver training like that to new CRAs?

S25: Like what sort of tools or what sort of setting?

M: Yeah, what sort of setting, like do you think a little CD Rom might work well or something over the Internet or something in person?

S25: Maybe something like that, I know workshops work well. I know when we go to NCI meetings they always have their workshops for the new CRAs and something like that might be helpful. Not everyone takes part in NCIs and if they didn't they would miss out on that. So maybe a CD, Internet definitely would be [yeah] that might be more, um, people might be more attentive to something like

that than a reading material. [yeah] That's why workshops are always good too because then there can be open discussion. [yeah]

M: And what would, what do you think should be the content of something like this, like what would be, you know, what should be covered?

S25: I think your scale was good, something to go over different questions you might ask yourself when assessing the causality. [okay, anything else?] I guess the reasons why, you know, go over the reasons why we do it, the importance of it. [okay, good]

M: Excellent, that's really helpful. Those are all the questions I have for you then, do you have any questions for me or any thoughts, final comments?

S25: No, it's definitely a challenging undertaking for sure so I'll be interested to see what you come up with.

M: So will I, no, that's great yeah.

S25: It isn't an easy topic for sure.

M: Yeah, I think it's, I agree, it's challenging but a lot of people have definitely shown a lot of interest in it. [that's good] So I think that there is a need there.

S25: There is, it's a difficult thing that's um, I would be more worried that it's being done properly so it might be helpful for sure. [yeah, yeah] (**worries about how causality is currently assessed**)

M: Good, well thank you very much for your time.

Subject 26

M: So I'll just explain a bit about what it is that we're doing then. As I mentioned, I am working with some researchers at the Juravinski Cancer Centre and we are very interested in how clinicians assign causality to adverse events in early phase oncology clinical trials, so specifically you know, Phase I. And um, but even the most experienced clinicians find assigning causality to adverse events challenging. And many groups expect prompt and sensible causality assessments. I'm sure as you know it's not always that straightforward and if done poorly there are implications. So we're interested in developing a tool to help clinicians more efficiently and reliably assign causality to adverse events during Phase I oncology clinical trials. And we feel that by better understanding your needs as a clinician we can make the tool more relevant and useful to you. You look like you had a question there. No, okay, so no questions then before I start? [no]. No, okay. So first I would just like to get a better understanding of the reasoning that you use, the thought process you use when assigning causality to adverse events. And I'm wondering if you can just recall a serious adverse event that occurred recently and just walk me through how you assigned causality to that.

S25: Okay, let me think, um, I'm just trying to think of some patients of mine that are on clinical trials. Alright, well I had a patient on a clinical trial, who ended up getting admitted ah, she was on a clinical trial of chemotherapy plus, either a study drug or a placebo. And she got admitted following the first cycle of chemotherapy with ah, weakness, and um, dehydration, diarrhea and um, sort of new focal neurologic findings. And it turned out that on MRI she'd had a series of strokes actually that explained the new focal neurologic findings [sorry the new focal] neurologic findings. Um, so obviously because of the severity of the symptoms on admission, that was a serious adverse event. And the problem was assigning causality to either the chemotherapy or to the study drug/placebo or to both, or whether it was unrelated to anything. Um, we know that the diarrhea and dehydration is an expected toxicity of the study drug and so we thought that was a reasonable, you know, there was a reasonable possibility that that's, what had

caused that particular problem. The strokes we weren't too sure of, we thought that there was multiple things that could have contributed to that, including just the cancer itself which makes people more prone to these sorts of things. Chemotherapy which increases your risk for thrombotic events, but thrombotic events have also been associated with the class of, with agents in the class that the study drug was in as well.

M: What was the class?

S26: Angiogenesis inhibitors. And so we thought that there was a possibility that it could have been related to both chemotherapy or the study drug/placebo.

M: So in that case it could either be the study drug or it could be the study drug in combination with the chemotherapy.

S26: In combination with the chemotherapy or it could have been the chemotherapy itself or it could have been, I suppose it could have been unrelated. I mean patients with lung cancer who stroke, or who smoke are at risk of having strokes and so on you know. [was this a lung cancer patient?] Yeah a lung cancer patient, so there's always the possibility that this could have been bad luck and unrelated to anything that was going on at that particular time. And so, and also the whole fact that she was dehydrated and so on probably made her hypercoagulable again and again made her predisposed to thrombotic events and so on. So I suspect it was all inter-related, but teasing out you know which of those treatment things was ultimately responsible for the stroke was difficult and is difficult. [right] **(although all inter-related, it is very difficult to pin point the primary toxicity)**

M: Yeah, so when it's a constellation of factors [yeah] and trying to figure out which is *the* most important.

S26: Important and which is the one that is ultimately to blame, you see what I mean? And I don't think that, these are not, I don't think there's a right answer to that, I don't think that you could know with 100% certainty which of those, which of the factors is ultimately responsible. Because likely if you'd taken away any of them it may not have happened. [right, right, very tricky]

M: So what do you think would have helped you then in that, when you were making that decision?

S26: Well I guess you know, knowing what the baseline risk of somebody with lung cancer who's on chemotherapy of having a stroke in the middle of their chemotherapy. Like, how often does that happen?, you know what I mean. [mmm hmm] So is that something that occurs you know in a small proportion of patients anyway?, right. [right] Um, and what proportion of patients with lung cancer who are not on active treatment have a stroke?. You know, so that you can see the increased risk just with chemotherapy itself. And then what proportion of people on these, this class of agents stroke, and what proportion of people on this agents in combination with chemotherapy stroke? [mmm hmm] So I mean knowing, knowing that may have helped assign causality I suppose in terms of the balance of probabilities if the likelihood of having a stroke on chemotherapy is less than 1%. But if the likelihood of having stroke on chemotherapy and one of these drugs is 10% then it makes it much more likely that it's the study drug that's, you know contributing and so on. [yeah] At least in my mind that's how I would, how I would logic it out. **(copes with uncertainty through process of elimination)** [right] So I guess you know, knowing some background features of exactly how common certain toxicities are in untreated patients. Because you know bad things happen to patients with cancer even without treatment right [yeah] they do funny things all the time. And then what the likelihood is with certain chemotherapies, particularly agents in the class, in the same class as the study drug and then that might help. [yeah okay]

M: Is there anything else that might have helped you in coming to that decision?

S26: Not that I can think of at the moment.

M: Were there any other challenges that you've come across when you assign causality?

S26: Well I guess one of the things that I've always had a difficult um, thing to grapple with is that there are too many, often there are too many categories of relatedness. [okay] You know, like definite, probable, possible, unlikely or not, do you see what I mean? [yeah] And I think that those are fairly subjective definitions that will vary from person-person. You know, what I think is unlikely is not necessarily what you might think to be unlikely [mmm hmm] and so um, again the assigning of causality there could be sort of chance depending on the interpretation of the definition by the individual physician. I think you know, in some ways it might be better if these things were done by consensus rather than by one, one person. Um, [consensus among?] consensus among other people who do Phase I trials in oncology, you know what I mean? **(lack of team work/group cohesion)**

M: So that everybody who is an investigator on the trial comes together to decide?

S26: Not necessarily everybody on the trial but at least the investigator who is involved, plus the principal investigator, plus maybe one other person either from the cooperative group or whatever. I don't know, I'm just trying to think of ways, and I think it would be good too to decrease the number of categories and to make the categories fairly explicit in terms of what the likelihood is. [okay, alright]

M: What external pressures or influences have you felt from third parties when you're assigning causality?

S26: Ah, none [can you recall a time?] none really, I mean there's, the only pressure that you feel um, is the sort of sense of urgency of, because you know you have to fill out the SAE report within 24 hours and all this sort of stuff. You may not have all the information and you may make an original, you may make an assessment that subsequently you change or becomes clearer as time goes on that something else is in fact happening and you want to change your mind about something. Which is, which is fine and you do, do that but I think that sometimes, I don't know that you should necessarily have to assign the causality right away. I mean I think reporting the SAE right away and saying this is what's happening and we're monitoring the patient and these are the steps we've taken. And we'll, you know, as things evolve we'll let you know what we think actually happened, rather than saying yes we think this is study drug related within the first 18 hours when you don't, you may not necessarily have all the facts yet. [right] **(finds time constraints to limit accuracy of assessment)**

M: Now would you tend to, would you say that you tend to be more cautious initially when you don't have all the information? Or are there you know, any kind of guidelines that you follow when you have to make that initial assessment under that time pressure?

S26: No, I mean, cautious, by that do you mean more likely to attribute?

M: Yeah, like, I've done over 20 interviews now and one of the things that I'm kind of gathering from speaking to people is that they tend to err on the side of caution in the interest of patient safety. [yeah] And I guess I'm just wondering where there is that time pressure, that 24-hour time where you have to report and assign causality in that timeframe and you don't necessarily have all the information. Are you more likely to say yeah it could possibly be related to the drug but we just don't know yet? Or, or are you more likely to say well I'm not ready to attribute it to the drug just yet because we don't know, you know?

S26: Yeah, I don't know that I necessarily go either way [yeah] I mean I try to look at what has happened and look at what is known about the drug and what the drug has been reported to do in the past. You know, if it's a fairly typical toxicity of the medication, like if the person has been admitted with diarrhea and dehydration and that's, that's a known side effect of that class of agents then I'm more likely to say, yeah that's probably what it is, it's probably drug related. Whereas as if, if, it's something like a stroke and I don't really know what's happening or what's going on and that's, that may have been reported in the past with that class of drug, but it's highly unlikely, highly unusual or whatever. I mean, I would, I would go more with what's already been reported for that class of agents. **(copes with uncertainty by assigning similar causality attributions)** [right, okay] Um, so, I mean obviously patient safety is paramount but I, I've not been in a situation yet where I think something is definitely drug related that has profound safety implications, you know what I mean, that, that really the trial should be put on hold. You know, these sorts of things because I think this is a toxicity that's definitely related to study drug that could be you know, life threatening to other patients.

M: Have you ever worked on a trial where it's been halted because of safety issues?

S26: Oh yeah.

M: Can you give me an example or tell me a little bit about that?

S26: Well ah, well I mean one of the, the clinical trial that I talked about before was put on hold by the data safety monitoring committee after they looked at the first bit of data to decide that you know, perhaps the toxicities were too great.

M: Which trial was that?

S26: BR24.

M: Okay, which drug was that using?

S26: It's using an angiogenesis inhibitor. [okay]

M: So that trial was put on hold. [yeah] And has it restarted?

S26: Now some of this information is confidential. [yeah] Yeah, the trial has, the amendment has been approved and it's been approved by Health Canada and the Data Safety Monitoring Committee and all that sort of stuff and the trial is up and running again. [okay] With an amendment obviously to try to protect patient safety. [okay, right]

M: But I guess that just sort of happens if you're not expecting certain toxicities.

S26: Yeah, I mean I think that's the whole point behind having a Data and Safety Monitoring Committee right? [right]. In fact it was the investigators, it was us, that asked for an earlier review of the toxicity because we felt that perhaps we were seeing too high a rate of toxicity compared to what one would expect from the chemotherapy regimen itself. So we thought that the study drug was probably adding a certain degree of toxicity that perhaps wasn't safe. [right]

M: So you guys actually asked for an early investigation of it [yeah] before the Data and Safety Monitoring Board caught on?

S26: Yeah, they weren't due to meet, we'd asked for an earlier review and we'd let them know that we were concerned so that they would look at the data with greater care. [that's good] Yeah, so I think that you know, investigators are, are highly attuned to the need for, for vigilance in patient safety. [yeah, yeah, okay]

M: So you talked about the sense of urgency in terms of assigning causality to the adverse event within 24 hours. Any other influences or pressures that you felt?

S26: No, I've never been ah, I've never been asked to change my causality or anything like that you know. [okay] Um, you know, sometimes people will ask for clarification and say you know, is this what you mean?, is this what you really think happened?, you know that sort of stuff, that sort of stuff. But I don't call that pressure [mmm hmm] I just see that as people seeking to understand you know, my, my line of thinking and logic and so on. [yeah, okay, great] **(has no issues defending their causality attribution)**

M: Do you have any concerns about how clinicians assign causality?

S26: Well as I said I think sometimes it's arbitrary and it depends upon the physician's interpretations of the definitions of you know, these different things. I think it depends a little bit on the physician's past experiences, expectations and biases with respect to the class of agents and so on. And I think that if you are unfortunate and the first couple of patients that you have on um, on a study or with a class of drug happen to have significant toxicity, which occasionally happens. Then I think that your viewpoint might be a bit skewed, which is why I think that having you know, a consensus approach to, to building you know, relatedness and so on may be better. Because you'd be able to have other people say well actually I've given this drug at that dose to this type of patient and so on and haven't seen that, so maybe there is something else going on. Or maybe it is a true toxicity related to this drug but it isn't as common as you would think and, and so on. I think hearing other people's experiences with a similar agent will allow you to put what's happened to your patient into a bigger context. [right] **(subjective)**

M: Now some participants have actually mentioned that sometimes the communication isn't that great among investigators in a trial, would you tend to agree with that?

S26: Yes.

M: Yeah, you think that could be something that could be improved?

S26: Yeah, and again I think that's where it gets down to the whole you know, consensus building approach to looking at toxicities and so on.

M: Can you think of anything else that might help in terms of, like you said putting that SAE into a broader context, so being able to sort of step outside of your personal experience and look at you know, look at it from a broader entire trial or drug history you know perspective in terms of the history of the drug and the trial that it's been used in thus far, that kind of thing.

S26: Yeah, I know, it would be interesting if you could do some sort of database search or something yourself, you know, and say okay look there's been x number of reports. But I mean, I doubt any drug company in the world will allow you to do that. You know, I'm sure all that stuff is kept very, that's all closely guarded secrets. [mmm hmm]

M: Now as I mentioned, we're looking to develop a tool that's going to help investigators in assigning causality. Um, what, what are some of the key features of a tool that you would require you know, for it to be useful and practical for you to use?

S26: Can you give me an example of what you mean?

M: Well I just know that you guys are really busy and some people have said you know, it can't add to my administrative burden. You know, I guess I would like to get a sense of if we were to develop some sort of a tool how would it best fit into your day-to-day working environment. [right]

S26: Well I think that it would have to be ah, clear and you know, I think that the, the definitions would have to be you know, not really subject to a lot of inter-investigator interpretation, you know what I mean. So that what I think is likely is the same as what you think is likely and so on, based on the definitions. [yeah] I think that it would have to, ah, I mean, I don't know, either like a little pocket card from a practical point of view [yeah, sure] that would be sensible you know, but not overwhelming. Right, I think it has to be simple and either you know, a pocket card that you whip out to look at the rule. Or you know, you can get on the Internet or you know, on your computer or something like that. It would have to be something that, that is not complicated and could be understood by everybody involved in the clinical trial, not just the investigator but the, the research nurses and research associates and all that sort of staff as well. **(tool needs to be simple, efficient and accessible if it is to gain popularity)** Um, like what sort of tool do you foresee? [okay] if you told me that then I could tell you, you know how I could see that fitting in. [mmm hmm]

M: Well one of our thoughts was, I don't know, are you aware of any decision making tools right now?

S26: Well I know that A gave a presentation once and he did say that there were some sort of algorithms to follow but they're not sort of widely used in oncology. They're, you know, it talks about you know, does it make biological sense, you know, these sorts of things and has it been described with this drug before and is there a rechallenge phenomena. I can't remember all of them.

M: And have you ever used those tools?

S26: No. Again, I don't know that anybody does in oncology. Have any of your, other than A, have any of your other people said yes? **(feels no tools are used in oncology clinical trials)**

M: No, no. [laughter] And in fact, you know, thinking back to their medical training and whatnot they're not even familiar with them. This one was developed by a fellow researcher named Naranjo and what I'd like to ask is if you wouldn't mind just reading over these 10 questions and crossing out any that you feel are not relevant to the Phase I clinical oncology setting. The idea was that maybe we might be able to slightly modify the Naranjo tool and make it more applicable to the oncology setting. [pause] Okay, that's great and then with the remaining ones if you could just rank them in order of importance, so 10 would be most important and then you can just kind of work your way down from there. In terms of you know, factors that you consider when you're assigning causality. Ones that are more important, there are probably some that are more important than others.

M: Great, okay so you crossed out number 6, that's pretty common, most people cross that one out. And then number 8, was the reaction more severe when the dose was increased, you crossed that out obviously because [you wouldn't do that] that rarely happens in Phase I right.

S26: Yeah, I mean that would be if you thought there was a possibility that they'd suffered an adverse event related to the drug, I think it would be unethical to [yeah] give them a higher dose. [laughter]

M: Absolutely. Did the patient have a similar

S26: But you don't have to, but less severe when the dose is decreased, I think that might be okay [mmm hmm] do you see what I mean, just half of the question. [yeah that's important good] Yea.

M: And then did the patient have a similar reaction to same or similar drugs in any previous exposure. I guess you're thinking this is a brand new agent

S26: Right, it's unlikely that they would have seen it and you know, the, um, I was just thinking that, one of the things that was going through my mind that this was first cycle toxicity you know what I mean. And so they wouldn't have had [previous] previous exposure, see what I mean and so that doesn't seem particularly relevant to Phase I. And I mean, usually patients aren't allowed to go on some trials [right] if they've had a similar drug in the past, you know what I mean, so. [okay, good]

M: And then most important to you was whether there were conclusive reports, previous conclusive reports on this reaction. Um, what did you interpret that to mean, sort of previous conclusive reports?

S26: Um, I just thought that that meant that it was established that you know, that there was a toxicity profile of the drug and that it, it's known that this drug can do x, y and z to patients. And if the patient had y and it's been described that x, y and z have happened then that, that for me goes a long way in saying okay, well this is a reaction that's known to happen with this drug.

M: Okay, so then are you thinking it would be in the IB [yeah] consent form.

S26, Exactly, exactly, that's stuff that's known about the, the agent already. [okay, great, alright]

M: And then least important, was the drug detected in the blood in concentrations known to be toxic, why was that?

S26: Because you don't get that information for ever, I mean, when, when um, like you may do a lot of pharmacokinetic studies with blood draws and so on but those samples are batched and sent off to God knows where to be analyzed and you don't see that data for months. [right] And so it's not relevant to actually assigning the causality at the time the event has happened.

M: Yeah, yeah, quite a few people have actually said that, okay. And then was the adverse event confirmed by any objective evidence, again that, that's a vague term isn't it, objective evidence?

S26: Yeah, and I'm not sure what they mean by that. To me if a patient complains of a symptom that to me is sufficient, I believe what patients tell me [yeah] I mean if they say this is happened to them I don't necessarily need objective evidence.

M: What would you consider objective evidence [well] if you actually see it happen?

S26: Well yeah, exactly, like I don't need to watch them vomit to ah, you know, what I mean. If they tell me they threw up 10 times, then they threw up 10 times. I mean people may exaggerate a bit but if they say they threw up 10 times then that's good enough for me, you know what I mean. [right] Now obviously if something really weird has happened like the patients had an MI and some selective drug causes cardiac ischemia or you think that that's what's happened then obviously you'd want to check for evidence that that's actually what's going on. But for the most part a lot of this is going to be symptomatology and your, your physical examination of the patient [okay] so, so I don't think you necessarily need anything more than, than that.

M: Was there anything on here, that wasn't on here that you thought maybe should have been included or anything that was missing?

S26: Not that I can think of at the moment no.

M: What did you think of it in general [this, tool? I think that] what was your first impression?

S26: I think, well I think it's actually the um, I mean these are things that we, I think go through in our minds anyway without, without necessarily having it quite so systematized as this. But these are the types of things that I ask myself right, like is this known to happen with this drug? is the time sequence right? Like obviously if it started before the drug it's probably not the drug unless it got worse, you know what I mean. [mmm hmm] You know, did it get better when we stopped? if we rechallenged the patient did it come back? I mean these are all, those are all sort of common sense things that we probably work through in our minds anyways. [mmm hmm]

M: So in terms of this as a tool, what do you think [I think] worthwhile or?

S26: Well the only thing about it is it, if you could somehow link it to the different categories of causality, see what I mean. Like if you felt that some of these were worth more points than others, see what I mean. And then you could um, you could say okay if you answered these yes, no, maybe, for a yes you get 2, maybe you get 1, no you get 0 and if you add up all the points and if you come up with a score of between this and this then it's probable. And if you come up with a score between this and this then it's possible, you see what I mean. [yeah] That would be the way I could see that because again unless you can, I mean if, a tool to me implies that there's a measurement like afterwards, or some sort of hard end point. Um, but if you go through this and at the end of the day it's still up to the investigator to make a judgment call having used that, then, then I don't know if we're any further ahead. Do you understand what I'm saying? [yeah, definitely] Um, so unless you can get people to interpret this all the same way and, and

then translate the answers to those questions into a measurement that you then apply to the event so that you come up with a probability statement. Like it's x% likely that this event was caused by the drug, then I don't know that it would change anything about our decision making now. I think the one thing that has to change that would help the most is the time pressure. Like I think that whole 24-hour, like I understand that we need to report the event but I think the causality part of it should be delayed until after you have the facts. And then you can say okay really I think this is you know. **(good idea reporting event, then assigning causality later, when it is more clear)**

M: I guess the challenge with that is though, you know the safety letters, the regulations state that if it's serious, unexpected and causally related then a safety letter goes out to all investigators [yeah] in all trials with the drug right. [yeah, yeah] And I guess that's why they need that causality assessment [right] within that first 24 hours. [yeah] So that would be tough to change.

S26: Well that would require you know, [ICH guideline changes] yeah, and I appreciate that. I'm just saying that, that actually, and I recognize that's for patient safety and of course therefore you should err on the side of attributing it to the drug. But I'm not sure necessarily that's best for science and the best for, for your purposes in assigning causality. [yeah, yeah, agreed]

M: Alright, the last thing I want to ask you about is, can you tell me about any training you've received specifically with regard to assigning causality to adverse events. How did you learn how to do it?

S26: Trial and error I guess. I mean the only, the only lecture I've ever heard about is, I've heard A speak once, but other than that you know, really nothing. I mean you'd ask other more senior investigators what they would say for this particular event and so on. But otherwise, there was no formal training. [yeah]

M: Yeah, that's what I've heard. Now do you feel that that's something that would be useful?

S26: Um, I guess, but are there, is there a consensus out there on how to do it anyways?

M: Well exactly, first you need to know what to teach people right?

S26: Well exactly, I mean, I mean, who would teach what, you know what I mean. Yes, I think all investigators should be taught how to do it but if there's no agreement on how to do it and if there's no standardized way of doing it then what's to teach? [yeah] So A can become the world's expert and teach us all and if we all agree on how to do it I think that would be great. Um, but until that time then [fire alarm] that's okay though, when it speeds up then you think about packing up and then there's a third level where you really should get out of the building. [laughter] So we're alright for the moment.

M: Right, we have these go off in our building too. And actually it's good because we're done now, so thanks very much, I really appreciate the time.

Subject 27

M: So as I mentioned assigning causality to adverse events is sometimes challenging, even for the most experienced investigators. And um, but groups such as industry sponsors, clinical trial cooperative groups, research ethics boards, they all expect prompt and sensible causality assessments. But I'm sure as you know, it's not always that straightforward and if it's done poorly there are some implications. So we're interested in developing a tool to help clinicians more efficiently and reliably assign causality, specifically during early phase oncology clinical trials. And we feel that by better understanding your needs we can make that tool more relevant to you. So do you have any questions then [no] before we get started? So can you think back to maybe a recent serious adverse event that has happened with one of your patients? If you could just recall a

serious adverse event for me, tell me a little bit about it and how causality was assigned to that serious adverse event.

S27: Um, unfortunately working with the brain tumor patients they end up being hospitalized due to their disease more so then they do to um, a drug related SAE. [right] Um, I'm just trying to think of, there was one patient a while back, a head and neck patient that was admitted to hospital and it was drug related SAE. It had to do with gemcitabine and it was documented in the investigator brochure that this was a potential AE that could happen.

M: What was the AE, why was the patient hospitalized?

S27: She, um, you're testing my memory [laughter] um, I can't recall the specifics.

M: Okay, but it was an expected event.

S27: It was an expected event.

M: So it was in the IB for gemcitabine. [yes] Was the patient receiving just gemcitabine or were there other.

S27: No, they were just receiving gem.

M: Okay, and in that case did you assign the causality or um?

S27: I, I anticipated what it was but I confirmed it with the investigator before [right] yeah, before putting it on the report.

M: So is that usually how it works then?

S27: Yeah, unless it's very blatant, um, we usually go over those types of things with the investigator just to make sure. It's their ultimate responsibility, so I want to make sure that they're in on the whole thing. [yeah, okay]

M: So obviously in that case you referred to the investigator brochure [mmm hmm] were there any other resources you referred to?

S27: Well in the protocol as well they usually list um, what the expected AEs can be and um, so that, that's usually my first, the first place I go to, the protocol just to review what they have and then if, if I don't get the answer then I'll go to the investigator's brochure. [okay]

M: And um, are there any other tools that you use when assigning causality, decision-making tools to try to determine whether it's due to the drug or due to other factors?

S27: Well usually when we set up, like our sheets that we use, our CTO assessment sheets that we use.

M: What's CTO?

S27: Clinical Trial Office, it's just, it's just our own [lingo] lingo yes. It's an assessment sheet that we use and usually when we're starting up a new study we refer to the protocol and we can use our own add or subtract whatever we want on these. So on the backside of the sheet we have AEs, so nausea, vomiting, fatigue, you know, the standards. And then if there is anything specific to the study that we need to capture or keep track of then we add those to the sheet. So you know if I happen not to be in one day or something then somebody going to see a patient for me isn't going to miss um, you know, covering something so. So I guess in a sense that's a tool that we use to, to capture AEs, on an ongoing basis. [okay]

M: So your assessment sheets [mmm hmm] that you take into every patient visit?

S27: Yes, for that study, we customize them basically specific for the study. And then that way as I said then nothing gets overlooked if somebody else happens to see a patient for you. [okay, good]

M: What would you say are some of the challenges associated with assigning causality?

S27: I think the challenges would definitely be if there are multiple drugs involved if there is more than one chemo, certainly pre-existing conditions in a patient.

M: When you say multiple drugs involved, why is that a challenge?

S27: Well I guess just trying to determine which drug could be causing the adverse event, you know if it's, you know they could both be causing it, it could be one or the other so you need to do.

M: Now can you think of a time when that was the case when you needed to...

S27: Not particularly for myself because again head and neck patients don't get chemo very often [yeah] and if they do it's a single agent. With the brain tumor patients, again they get single agents so. But I do know with helping my colleagues troubleshoot when they have you know, chemo trials, particularly in lung patients, they would have you know, more than one agent that their patients are being treated with. And what they do again, with the assessment sheet is they, they would put the two drugs and have columns for each one so that they can, they can sort through it a little bit easier. [yeah] But unfortunately I guess I'm not a great candidate to be interviewing [oh no] because I don't do a lot of chemo so. [yeah]

M: That's okay, you're an experienced CRA that's exactly what we're looking for. Okay, so if there's multiple drugs involved [mmm hmm] sometimes that's a challenge, trying to tease out [yeah, yeah] which drug has caused it. [yeah]

S27: And pre-existing conditions in the patient if they have you know, other health problems that could be contributory to some symptoms. You know, and sometimes it can be as easy as just the person themselves, some people will say they're perfectly fine when they're not. And other patients will elaborate on you know, how they're feeling and might be exaggerating a little bit. So you know you have to try and understand the patient themselves as well.

M: How do you, well can you give me an example of maybe a time when that's happened in the case of an adverse event?

S27: Well even if you just say like, fatigue for instance, if you say are you feeling fatigued?, oh, oh yes I'm so fatigued. Are you having to take naps every day?, oh no, no, no. So you're getting, on the one hand they sound like they're flat out all day and then when you kind of guide, not guide them but you know you pursue it a little bit further then they end up saying oh no, I don't need to take a nap. [laughter] So you know, that's a pretty simplistic example but that kind of thing.
(patient's view is also subjective, need to investigate patient claims)

M: Yeah, that's a good example, okay. So yeah just trying to deal with those sometimes unreliable patient reports and I guess it's all based on...

S27: Yeah because for us, I'm not a nurse and when we go down to see the patients we're recording what they're telling us. So we're saying first of all, how have you been feeling in the last week? and some of them say 'oh feeling great you know, pretty good'. And then you look and see what they have commented on in the past and say well how are you doing as far as, last time we met you

said that you had this and this and this, how's that doing? Oh, it's the same, so then you're going okay, it's the same [laughter] and then when you read the doctor's progress note, all of a sudden they've divulged all this other information. You know, and some of those things, you know, could definitely be related to treatment that they haven't really, the patient really didn't comment you know, to you about because they didn't really think it was that important or significant or you know. [yeah, yeah] So just getting the right AEs down and I think the language of the AEs as well, you know, especially with brain tumor patients when you're looking at the neuropathies and whether they're like you know, you need to kind of break it down and make sure that you're all talking the same language. [okay]

M: So are there different terms for neuropathies?

S27: Well, you can have neuropathy or myopathies or there are sensory neuropathies so you know, there's different ways of, they're all very slight differences sometimes in, in the terminology.

M: Okay, so you just have to break them down to be more specific?

S27: Yeah, like if the physician calls it one thing and you're calling it something else but basically you're talking about the same thing you really need to pinpoint what terminology you're going to use so that there's consistency.

M: And do you use a tool to keep that terminology consistent?

S27: Um, not really, usually when I review the progress notes if he's calling it something different than I have then I'll go to him and say okay, what are we talking about here? [yeah, yeah] So they're very involved with us and they're really great about you know, clarifying different things. [okay, alright]

(unclear/inconsistent terminology)

M: Any other problems or challenges you've encountered when assigning causality?

S27: Um, I can't think off the top of my head.

M: Have you got any concerns about the way causality is being assigned by clinicians?

S27: Um, well I don't think there is ever going to be anything that's going to be black and white. **(grey area)** I mean I think that's, that's something that we have to live with. **(understands grey area is inevitable, copes with it)** And I think as long as you know, you're able to have those discussions with your PIs and, and make sure that again, you know, you're both involved in discussing the same points and talking the same language, then you know you can usually come to the conclusion. [okay] But sometimes it's never that easy, even for the investigators, sometimes they'll say, I don't know, and I'll say well you have to give me something, I have to report this you know, so, anyways.

M: What happens in that case when you don't know, is there a sort of general guideline that you follow?

S27: Well, we usually go back to, sometimes we'll go to the sponsor and say, this is the situation with this patient and this is what's happened and we're having difficulty determining. What do you want us to do? [right] And see what they [what do they usually say] well, if the investigator feels that it's this, that and the next thing, then that's fine, it's whatever the investigator says. That's usually their answer. [right, throw it back in your court] [laughter] Yeah.

M: And if you're really just not certain is there a category for that on the causality scale?

S27: Well yeah I guess, because I think they have probably, or possibly or so sometimes you're stuck between possible or probable you know [and you're just not sure] you're stuck.

M: Now how do you determine if you're going to call it probable or possible, like what's the tipping point?

S27: I think again going back to the protocol or the investigator brochure and, and you know discussing it with the investigator and putting all the pieces together and seeing which category it fits into better.

M: Let's say it's not an expected event, let's say a patient has a serious adverse event that just isn't expected for this fairly new drug [mmm hmm] what do you guys do in that case? Then I guess the IB isn't very much help. [no]

S27: Um, well I, I think what, I'm just trying to think if I've had an occasion for that, um, hmm, I don't really know that I've had anything that hasn't been you know specifically a disease related event. Um, you know, as opposed to an unexpected, like if the patient developed neutropenia and it's not something that, that you're expecting. I don't think that I've come across that. [okay, alright]

M: I've done quite a few interviews now and one of the things that's come out is it is kind of difficult to make that distinction between probable and possible and how do you determine you know and I guess, that's sort of part of the difficulty. [yeah, yeah]

S27: And it will never be black and white, you just can't [no] you know, sometimes you just go with what fits best. And I certainly, you know, wouldn't make that determination on my own if it's something, you know, if they've got something like that where they've developed neutropenia where the drug isn't

going to give them that. Then that's something I would definitely go to the investigator and say how do you want to address this you know. [yeah, okay]

M: Now have you ever felt any external influences or pressures with regard to your causality assessments?

S27: No, you mean with sponsors or?

M: Just third parties, any pressures from?

S27: No, no, [no eh, okay]. I mean we have lots of discussions amongst our group if we're struggling with something like that we usually seek out you know, our colleagues opinions. But no, I wouldn't say I've ever had any pressure to, to call it one way or the other.

M: Or to change your causality assessment once you've made it?

S27: No. [no okay, good]

M: So from your perspective then what would make assigning causality easier?

S27: That's a very good question. [laughter] I, I don't really know, I think just, just having, like making sure that you know everything, you know, if you have a list of everything that is potentially um, likely to cause an AE or can cause an AE for that particular drug then you know, it's certainly a good tool to just have a look at and say okay, they could develop this, this and this. But again, we do have that information provided to us so [in the IB] mmm hmm. [yeah] So I don't really know, I don't know if there's kind of like, you know, those [algorithm?] algorithms that you can look at. I know, they do provide those too with some of the protocols, not usually specific to, well some of them are specific to their counts and different

things. If their blood counts are low, go here and do this and do that you know. [laughter] But I don't know, I mean the studies are becoming so complex.

M: Why?

S27: Well it's just the future, they're, they're looking, I think they're fine tuning research a little bit more now and they're um, you know, they're looking at, they're doing more testing on patients during the course of their treatments. And they're capturing more data during the course of the study and the demands are a lot more than they were before. And I think that it's um, I don't know it's just becoming a little bit more complex. **(a lot of content to report, assigning causality is becoming more difficult)**

M: Can you give me an example of some of the demands that have increased, do you mean for you?

S27: Well I think for all of us, um, I think the, well the number of tests and timelines and everything that need to, you know, you've got to meet, so many different timelines and um. [for what?] For eligibility for patients, um, like you might have, a patient might have to start treatment within 5 weeks of surgery but they only come to the centre their second week after surgery so now you're down to 3 weeks [right] to get them on. But you have to send tissue, pathology tissue off to Texas or something to be reviewed before you can put them on study [right] so there goes another, at least a week. And just with imaging, imaging is always an issue, trying to get imaging done in a timely manner. Um, but I mean I digress, that's not really the topic that we're on.

M: Yeah, but that's part of it isn't it? If there's anyway that you know, causality can be made simpler [yeah] then that allows you to focus more of your energy [mmm hmm] on the other increased demands. [yeah]

S27: I guess because the studies that I do, it hasn't really been, um, that, you know, that difficult for me, which thankfully. [laughter] But I know some people have a more difficult time. [yeah, good, well not good but] [laughter]

M: So when you say increased testing, like even before you know whether they are eligible [mmm hmm, all the pre-screening] pre-screening tests.

S27: So it could be blood work, MUGA scans, ECGs, um, CT scan, pulmonary function tests, you know, they're requiring a lot more up front now. And also specific imaging parameters, so if your patient, particularly with the brain tumor patients if they're required to get MRIs on a regular basis which they do anyway. But they want to have certain slice thickness of the image so they've got to, that has to be set up with the department. So there's a lot more you know, [right] they're getting really nitty gritty with the details, which is good. I mean now you're comparing apples with apples [yeah] because it's, it's, they're fine tuning it a lot more. [good, alright]

M: I'm just wondering if you would do an exercise for me and read over these 10 questions [mmm hmm]. This was an algorithm that was developed by a researcher named Naranjo. And if you could just read through those questions and cross out any that you feel are not relevant to the early phase oncology clinical trial setting. You think they're all pretty good.

S27: I think they are all pretty good, um. [okay]

M: So now if you wouldn't mind just ranking them in order of importance. So 10 would be most important [mmm hmm] and least would be and 1 would be least important. Just to get an idea of you know, which factors are...

S27: The only one that doesn't make a lot of sense to me is because you wouldn't know if the patient is getting a placebo, well I guess in some instances you might.

M: Right, just cross it out if you don't feel it's relevant.

S27: Well I guess it depends if you know if the patient has been given a placebo or not.

M: Yeah, and this is specific to early Phase, like Phase I oncology where patients aren't usually getting a placebo. [yeah] So, others have crossed that one out.

S27: Well this is, the drug, the toxicity one for the drug is important but a lot of times you don't have a blood test that would detect it.

M: I'm sorry number 7 [yeah] a lot of times you don't have?

S27: You wouldn't have a blood test to detect the drugs that are being given [okay] like was the drug detected in the blood?, well they don't have a test to detect it a lot of times [okay] you know what I mean.

M: Yeah, so you might want to cross that one out too I guess, I don't know.

S27: Yeah, probably because they don't have like. Well hopefully we wouldn't be increasing the dose if the patient had some kind of an adverse reaction [right]. I agree with the, if the dose, [the last part] yeah.

M: Okay, you can just cross out that part of it then if you like. Okay, so the one you ranked the lowest, was the adverse event confirmed by any object evidence?, [mmm hmm] and what did you interpret that to mean?

S27: Well I wasn't really quite, I was trying to think of, like putting that into um, a previous experience but I couldn't really think of anything that, that would really fit, so I'm not sure it that would fit for other.

M: So what did you understand objective evidence meant?

S27: Well if the patient had a rash or has something that you can measure, you know, something visible. [right, okay]

M: But that's not really too important to assigning causality?

S27: Well it's important but I don't know if it's, like something like that would be difficult because they could be getting a rash for a lot of reasons. [okay] But I don't know.

M: Great, and then all the others you felt were pretty important. [mmm hmm] Was there anything here that you felt was sort of missing, um, should have been included?

S27: Nothing really jumped out [no] I mean it covered a lot of bases, you know, if there was any history of any kind of reaction. That it was previously documented, that's important to know, like if it's in the IB. Um, and then the timing whether the event stopped after administration of the drug and that kind of thing. Am I missing something?

M: No, no, what did you think of this tool did you think it was?

S27: I thought it was good.

M: Do you think something like that would be helpful? [mmm hmm] What sort of, how would it be most helpful to you?

S27: Well just, you know just answering some of the questions that you, you know, sometimes you just get blinded by your tunnel vision you know, when you're looking at these things and, and it just brings things to the forefront that you might not think off the top of your head. [hmm okay] Makes you think. [laughter] [okay great]

M: So this, this was one thought was to just try to modify this Naranjo scale to incorporate you know, make it more relevant to the early phase oncology clinical trial setting. And um, yeah, okay, great.

M: And lastly I would just like to ask you about the education or the training that you've received with respect to assigning causality. [mmm hmm] So how did you learn how to do it?

S27: Let me see, um, I think just basically, you know, I was asked to do what I've been doing. You know, when you're developing, when you're starting a new study and you're developing your own tools, when you go to see the patient the adverse event page to include what the expected things are. And um, you know, certainly to review the protocol and usually I don't read through the IB unless I'm looking for, unless it's something that I've never dealt with before then sometimes I'll have a quick look at it to see if there's anything [unusual] yeah, unusual that I haven't come across. Um, and basically that's been you know, the rule of thumb, just to basically know your protocol and ah. **(knowing your protocol is key to feeling confident on the job)**

M: So who taught you how to do all that, or you know, did you take some courses?

S27: Well over the years I've gone to lots of conferences and things, but um, my, my supervisor when I first started you know, just in the, because I hadn't worked

in clinical trials prior to being here. So this was um, [sort of on the job training] on the job yeah. [okay]

M: Now thinking back to that time do you think it might have been good to have some sort of education around how to assign causality?

S27: I think so, I think that a lot of centers are um, lacking good training tools for new people coming in. For sure, I mean, because it is so important in research, you really do need to know what the causality is and um, I think that, yeah. I mean, I'd love to see real training programs throughout, like across Canada. And I hope NCIC will take something like that up. I know that they do, they're, they have good workshops you know at their Spring meetings and things. That would be an excellent place to present. [okay]

M: Alright, now if we were to provide some sort of training around assigning causality and that sort of thing, would it, do you think it would be best done in person, or over the Internet, as a CD Rom or at a workshop or a conference. Like what, what's your feeling?

S27: I think you would reach more people if it was, you know, if we could go to a Web to do it, um, the, the conferences are great but you only get you know, a small amount of people. Unless you have the CD to provide to them to take back to their centre, which is another option. Yeah, to maximize the number of people that you'll reach, I think it's best to do the Web thing. [okay, great]

M: As you know I'm here for a short time and today is my last day. Is there anybody else that you recommend that I speak to while I'm here?

S27: Who have you talked to already? I know you talked to M.

M: M, SG, yourself, I'm meeting with M this afternoon [okay]. If there are any other CRAs that you think might be interested and have a few minutes.

S27: I'll ask, I mean some of our more senior CRAs um, I will have to make sure they're here. I mean some of them just aren't, there's holidays going on but I'll certainly um, see. [okay great]

M: Thank you very much N that was wonderful.

Subject 28

M: I'll just give you a little bit of a background about what we're doing. I'm working with some researchers at the Juravinski Cancer Centre in Hamilton and what we're interested in is how investigators assign causality to adverse events in clinical trials, specifically early phase oncology clinical trials. And the idea is, if we can get a better understanding of how that's done and some of the challenges involved in that, that we can try and make that process a little bit better. And develop a tool to help make that, those causality assessments a little bit more reliable and consistent. And um, and so we feel that by getting this better understanding of the needs of medical oncologists and clinical trials associates like yourself we can make that tool more relevant to the people who will be using it. [mmm hmm] So do you have any questions then [no] before we get started? First I would like to ask you if you wouldn't mind, I don't know if this will be possible but if you could try and recall a serious adverse event that has happened recently and how causality was assigned to that event.

S28: I had a patient who, oh actually it's not even a GYNE study, okay so that won't work. [laughter]

M: It really doesn't matter what kind of study it was.

S28: It's a primary lung PET scan study that I'm doing and a patient, um, when they were brought into the recovery room after his surgery he had a stroke.

[okay] Um, so causality was, because the study was comparing PET scan for staging for surgical candidates for lung cancer, compared to conventional staging it was not related to, the causality was not related to the PET scan because it happened right after the surgery. [um] Is that what you're looking for?

M: Sure, it sounds like an interesting, because it's not a drug study [no it's not a drug study] so it confused me a bit. So I guess we're [you're looking for more drug studies] yeah, can you give me an example of a serious adverse event where a patient was treated with a drug, like an investigational drug?

S28: Um, okay, I had to go back a bit. [laughter] This lady was in a local study that we are doing for a medication and she started on the medication, I can't remember what day it was. But it was three days prior to being admitted to the hospital with a DVT, so of course it was temporally related so the causality ended up being probable.

M: Okay, and so that was based on the temporal relationship. [mmm hmm] Um,

S28: And the fact that there was no prior history of DVTs. [okay]

M: And now was that you that assigned the causality or um, or how did that go?

S28: When it comes to SAEs, I've always got in my head what I think it's probably going to be but I leave it up to the investigator to assign causality. [okay, great] **(doesn't mention collaborating with investigator to make a decision)**

M: So in that case, you were looking, you said there was a temporal relationship and you said the patient didn't have a prior history of DVT. Were there any other things that you considered when you, when you were assigning causality?

S28: Well those are the two big ones really. Um, of course you have the investigator brochure which gives you a hint of what to be aware of. And um, this was for an ovarian cancer study so sometimes they are a little more likely to develop DVT and thrombus. Um, so yeah, those were other things that were looked at but those were the two big ones were the temporal relationship of course and her past history. [okay] **(temporal relationship- theme for coping with uncertainty)**

M: So you mentioned you do refer back to the IB, are there any other resources that you look to?

S28: Um, the protocol will sometimes give you an idea, but not usually. Um, I like to have a look at the IB and of course the science reports and everything that comes in, the adverse events reports that we do get [safety letters] safety letters yeah. I look at those and make sure that everybody, like all the investigators have a look at them as well. But um, I usually go by the IB and the letters. [okay] mmm
hmm

M: Do you keep those safety letters in a database at all or you just, how do you look them up?

S28: How do I look them up? [yeah] Well for my GYNE studies they come to the principal investigator and he is very good about making sure that the other investigators see them and then they come to me. And then they're forwarded to ethics to do their thing with them and then they come back to me. So they're all filed in my office. [okay, that's good]

M: And that system seems to work for you?

S28: It seems to work yeah. They weren't really doing that as diligently when I first started, but um, they do now. [laughter] [that's good]

M: Do you use any other tools to help you when you're assigning causality, flow sheets or decision trees?

S28: With the GYNE studies no. With my PET scan study, the other one we were talking about briefly does have a decision-tree, so I find that helpful. **(would consider an algorithm helpful)**

M: And what is the decision tree for?

S28: Um, for assigning causality and if they want it reported as an AE or an SAE and how quickly they want it reported. [oh I see] Because it's very odd the way that study is working in my head, so I follow their tree that they provided because it doesn't seem as logical to me they want it done. **(lack of understanding between parties)**

M: So that has more to do with how quickly to report and where to report, that kind of thing?

S28: And what to report, what to report as adverse events, AEs and SAEs, yeah. But no, none of the GYNE studies have any aids. [okay]

M: What are some of the challenges you've encountered when assigning causality?

S28: Well, most of my studies are also sponsor studies and they tend to make the wording vague on purpose. **(big statement)** [laughter] Probable, possible [the wording of what] probable, possible, definitely related, possibly related all the, so sometimes that can be a challenge if it's something you haven't encountered before. [mmm hmm] Um, but as I say it, anything, if I'm assigning a causality to something I'm making sure the investigator knows what I'm doing.

And if I have any questions about it then the final decision is always up to the investigator about the causality.

M: So you said the wording of those terms on the causality scale are vague [mmm hmm] and that's sometimes a challenge when it's something new that you haven't seen before. [mmm hmm]

S28: Yeah, something unusual.

M: Why is the wording, like can you tell me?

S28: Well usually the wording is not related, possibly related, definitely related, are usually the four main ones that they use, so it depends how much you read into these things too sometimes, how you're going to interpret them. So I find sometimes that wording can be tricky, especially possible, probable when you're going into that area. **(need for a standardized scale)**

M: Do you have any general guidelines that you follow, you know, what's a possible and what's a probable?

S28: Um, of course the temporal relationships and the past medical history are the two big ones that I look at. Also again, back to the investigator brochure and what's been reported before will help um, determine if it's possible or probable if other areas, other centers have seen it happen before or if it's already a known in the IB. [okay]

M: So if it's known, then it would be a probable, is that how you do it?

S28: Yeah. If it's known that it's happened before, um, especially with um, things a patient hasn't had before, it wasn't pre-existing then it's probably related, yeah, if it's already been reported elsewhere. [yeah]

M: Yeah, other people have told me that they find the wording pretty difficult to wrap their head around and not really sure what the meaning of those terms are and, yeah I think there's room for improvement there, maybe even just to define those terms a little bit better. Or you know, here's when you use possible and here's when you use probable. [mmm hmm]

S28: But then even doing that, because you're looking at such a broad category of what needs to be reported, that's not even going to be easy to work. Like good luck coming up with something like that. [laughter] [thank you, well we'll try] Because it's hard to pigeon hole and that's exactly what we're supposed to be doing and you're always going to come up with situations that aren't going to quite fit and then what do you do? And that's why I think it was designed a little on the vague side is to take into consideration those things. And I haven't had it happen here, but in my past life as a coordinator before I came here, um, I would often get um, queries back from sponsors about AEs. Saying well you've marked this at possible but we think it should be probable, what do you think about changing this? and vice versa we think it should not be related because it's not here dah, dah dah. Like I've had that happen in other areas of research where I've worked, I haven't had that happen here yet. [yeah] But so they end up, you don't know if they're doing this, the sponsor is doing this because they have better information or they're trying to um, I hate to say manipulate the data or the outcome. But you know, that's kind of in the back of your head too. **(unsure of investigator's intentions at time, perhaps a lack of communication)** [yeah] But as I said, I haven't had that happen with oncology but I've had it happen in other areas.

M: Where they've asked you to change your causality assessment. [mmm hmm] What did you do in that situation?

S28: Well where, when I worked there I didn't touch causality, that was the investigators job. So we would discuss this patient had this and, dah, dah, dah and that's what happened and what do you think? and I would have him do it. [yeah] So anytime they asked for anything to be changed I would leave those queries up to him and 9 times out of 10 he would not change them. [oh that's good] Because, but then it gets annoying and then you start to second guess and wonder why are they even asking if the investigator is ultimately responsible for the data and not some data entry person a million miles away who has no idea what is really going on. Why are they second guessing this, what are they really after? [yeah] **(uses the term annoying, again feels disconnection with sponsors)**

M: Have you felt any other pressures or influences [nothing] from third parties.

S28: No, and as I said this wasn't in oncology these were in other areas of research.

M: What are your concerns about how causality is being assigned now?

S28: Well other than the wording, I think that was the big one and off the top of my head can't think of anything else. [okay, okay] **(issues with terminology)**

M: And from your perspective what would make assigning causality easier?

S28: Better guidelines if they can be developed. [for what?] As you mentioned before, about what exactly do you mean by possible, probable. Um, a decision tree that would be followed when a patient reports, although that would be a forest not a tree. [laughter] Some, just a better definition of exactly what the sponsor means by those terms would be helpful. [okay] Because even if you have questions about it, um and you try and talk to your monitor, it's not their

decision either, so they don't help you. [yeah] Because they can't be influential in that regard. [yeah, okay]

M: What I'd like to do now is just ask you to read over the following questions. These 10 questions were developed by a researcher named Naranjo and it's an algorithm to help in assigning causality. What I would like you to do is first just read them over and cross out any that you feel are not relevant to the early Phase, specifically Phase I oncology clinical trial setting.

S28: I've never done Phase I.

M: So you've never done a Phase I? [no] Just early Phase, Phase I, Phase II, when you read it you'll [okay] it should be okay for you to do. Are there any that you would cross out?

S28: No. [no okay]

M: So then now would you um,

S28: See this is how it gets confusing. [laughter]

M: So now then if you could just rank them in order of importance. So 10 would be most important and 1 would be least important. Just to get an idea of what factors you feel are more important than others. Okay, [mmm hmm] great, that wasn't too hard was it, no, okay.

M: So least important was number 1, did the adverse event appear [oh, oh oh, I did it wrong] did it backwards, okay. That should be easy to fix. Perfect. Yeah, okay, so did the adverse event appear after, so that was most important to you then. And least important was did the reaction reappear when a placebo was

given. Um, good. Now what did you understand objective evidence to be, to mean?

S28: Um, objective evidence to me would be the blood work, um, that would be the big one. And if, [blood works showing?] yeah and what type of reaction did the patient have, did they break out in a rash, did they swell, did they have shortness of breath, did they have trouble breathing, like what, what happened, did blood pressure go up? Things like that.

M: Alright great, good stuff. Now was there anything here that you felt was missing that should have been included? What did you think of it overall as a tool?

S28: It didn't take anything subjective into consideration. Um, now you were looking mostly for SAEs, see SAEs are much easier than AEs to assess. **(tools can be too objective)**

M: Okay, why is that?

S28: Well because AEs it depends on what the patient tells you and it depends on the patient what they're going to tell you. [right] And you know if it's, it really depends on the patient, what they're going to tell you. But um, that can have a big factor too in collecting information is what the patient tells you and if it's AEs. **(patient variation can alter causality attributions)**

M: So, so some patients tell you more than others or?

S28: Oh yeah [laughter]

M: Why do you think that is?

S28: No idea.

M: Can you give me an example of a case where that has happened?

S28: I had one patient, again, this is in my past life as a researcher, filling out a diary card for a once a day allergy medication and come back in a week with your diary card. And he came back with an itemized daily list by time of what he did [oh my gosh] for his entire day. We took the dog for a walk, we walked this far, turned at this time, had breakfast, this is what I had for breakfast, this was when I finished breakfast. [laughter] It was unbelievable. [he did that for a whole week?] Oh he did that for the entire six weeks of the study. [oh wow] Yeah [that would have been a lot to read] It's a lot to read and then of course you know, he said that you know this day he got up and he stretched and felt a pain in his back so that's an AE, you know and it's just, some people can be a little nutty.

M: So some patients tell you absolutely everything. [and others tell you nothing] Right, okay. So that's what makes it difficult I guess. So you said that is tool doesn't include anything subjective, so what do you mean by that?

S28: Well from the patients point of view, you're not, you're not asking the patient. But I understand you're looking at an acute event here, not um, like the patient goes home and 6 hours later develops a rash, that kind of thing and doesn't tell you. Or you know, develops abdominal upsets, nausea, vomiting or anything like that, which can happen after a drug administration but not possibly within the timeframes you were looking at in this tool. You are looking more at the AEs that can later develop to an SAE if they become dehydrated and have to be admitted.

M: So you think this tool would work better in the serious adverse event rather than the adverse event setting. [mmm hmm] Okay, yeah, that's a good point.

S28: With the GYNE trials you are giving chemo meds, the patient is here for 3 hours, they go home. The next day they start to feel really nauseous, start vomiting, stay at home, don't tell anybody, just take the medications you give them, the medications aren't working, they stop drinking. Three or four days later they end up going into emergency, being put on IV fluids and admitted, that happens, that happens. [right] So that wouldn't capture that situation at the time, because this to me when I read this was okay, you're talking mostly in the timeframe when the drug was given. [mmm hmm] So, you know, things happen later that start out as adverse events then become SAEs and that, that didn't seem to fit here. [okay]

M: Now do you think something like this would be useful?

S28: Yeah. [laughter]

M: You don't sound too convincing.

S28: No. It would be useful but um, some of it's kind of redundant and it's a little too wordy to be really time efficient useful.

M: What's redundant about it?

S28: Um, well how many times are you going to have a reaction and then give a placebo? Like you're not going to be switching arms if they're in a study. So I didn't think that really applied. Um, this here was the reaction more severe when the dose was increased, or less severe when the dose was decreased, ah when the dose was discontinued, so these are very close. [number 3 and 8] And 4 when the drug was readministered, so these are all very similar. [mmm hmm]

M: So if it could be shortened up [mmm hmm] and made a little less wordy it might be more useful. [mmm hmm] Do you think you would use something like this?

S28: Possibly. [laughter]

M: You don't have to be kind, you can tell me "I would never use this".

S28: Well I wouldn't use it in this form, definitely not, it wouldn't be worth my time. But if it was shorten up, more concise and possibly covered later Phase SAEs then yes it would be more useful than the way it appears here. [okay good]

M: The last thing I want to ask you then is a little bit about your background in terms of how you learned how to assign causality to adverse events. So can you tell me about any training that you received.

S28: I guess most of the training was at investigator meetings [yeah] yeah.

M: Okay, and what did they teach you?

S28: And I think nursing background, it's something you just kind of learn after nursing for years.

M: And what did you learn at the investigator, what did they teach you about at the investigator meetings?

S28: Well they go over um, SAE reporting and that kind of thing. So I found that a little helpful when I first started doing clinical trials. But now it's the same stuff every week, it's redundant. [yeah] Yeah, but I think most of it was just nursing background.

M: What additional education about assigning causality do you feel needs to be made available?

S28: Well, honestly, I don't think we should be doing it at all, I think that is the investigator, they're ultimately responsible, so I don't think coordinators should be assigning causality at all. [okay] Um, but that's just my opinion.

M: So then, so that means that there shouldn't be any education about assigning causality is that what you're saying?

S28: Well I think the investigators should be educated [yeah] on a lot of things. [laughter] So if you're looking at education, my point of view is that coordinators shouldn't be assigning causality. Um, but the investigators should definitely be educated in how to do it. Does that answer your question?

M: Yeah, great, I think that's a good answer. Well I think those are all the questions I have for you today. [okay] Thank you very much [no problem] I really appreciate the time because I know you are very busy.

Subject 29

M: I'll just explain a little bit about what is that we're doing. [mmm hmm] As I mentioned I'm working with Dr. AA and B who is the manager of clinical trials at JCC and with two other investigators in Hamilton. And we're quite interested in how causality is assigned to adverse events in early Phase oncology clinical trials specifically. [okay] And our interest is in this because we would like to eventually develop a tool to help make it a little bit easier. [okay] So as I'm sure you know, even the most experienced clinicians find assigning causality [difficult] difficult. And many groups such as industry sponsors, clinical trial cooperative groups, research ethics boards, they all expect prompt and sensible causality assessments. [mmm hmm] But it's not always that straightforward and if done poorly there are some implications. [right] So as I mentioned, we're interested in

developing a tool to help clinicians make it more reliable and efficient. And we feel that by better understanding your needs we can make the tool more relevant to you. [okay] So do you have any questions about what we're doing [no] before we start? First I'd like to start by just asking you if you could recall a serious adverse event that occurred with a patient where assigning causality was fairly straightforward.

S29: Well it's, I mean we see many patients who develop febrile neutropenia for instance from a chemotherapy drug and in that case it's fairly straightforward. That's an expected adverse event in many of the chemotherapy drugs that we use. Another one that would be a good example is if someone develops a blood clot and they're on tamoxifen or that class of drugs in a study, that also um, is a well-known toxicity or side effect from that drug. So those would be two examples. [okay]

M: What about, can you give me an example of a serious adverse event that happened recently that you can recall and you know, assigning causality wasn't that straightforward, wasn't that easy.

S29: Um, I think, when we look at the reason why people are admitted to hospital, probably one of the ones that we get stuck on are, um, people who may have neurological types of events. Such they may um, be admitted to hospital with, not exactly, not stroke like symptoms but um, well for instance if they came into hospital, and this isn't an example I've seen recently, but if they came into hospital with meningitis-type symptoms and you're wondering whether it's entirely meningitis or could it be leptomeningial disease from their cancer and so on. And so for instance in the breast and lung cancer population we do see people who um, present with neurological symptoms that could be part of their disease and/or outside of their disease it could be an infection. Or are those symptoms related to the study drug? Particularly if you can't prove that it's related to the, it's related to the disease. So if you, if they had these symptoms and you do imaging such as

an MRI and it's not positive and if you do all the normal tests and they're negative, sometimes it can be hard to assign a causality particularly if you're using a newer drug, so neurological type presentations. **(newer drugs- harder to assign causality)** Um, another sort of classic one that we see in a lot of cancer patients is weight loss, you know, weight loss, low grade fevers, fatigue. These ones are really difficult, because if they're admitted with a generalized um, decline in their performance status, so they're weak, they're dizzy, they've lost weight, they have poor appetite and they're on a study. Is that part of the disease or is that part of the treatment that they're getting? And I have an example, this person wasn't on a study but he had lung cancer and was getting gemcitabine and carboplatinum and he was very weak and dizzy and losing weight and so on. And the question was, was that his treatment or his disease? and when we stopped his treatment he actually got a lot better. So by stopping the treatment we sort of defined that it was the treatment and not his disease. But I think those constitutional symptoms that cancer patients get are the hardest ones to try and delineate disease versus, versus drug. **(confounding variables)** [right] Another one of course that I can think of would be pain, different types of pain, whether it be visceral type pain or neuropathic type pain um, that someone ends up in the hospital with for instance a pain crisis and is that pain crisis related to their cancer? and sometimes that can be hard to sort out. Or is it something that the cancer drug that you have given them has done to increase the pain? For instance what happens if the cancer drug has caused them to bleed into a tumor and that, that has actually caused pain, for instance if they've bled into liver metastasis and that has stretched the liver is that what is causing pain, those types of things. So I think pain is a common thing that we see that can cause people to be admitted to hospital for which who knows? **(very complex, left with uncertainty)**

M: That's interesting because some people have given me an example of pain as something that's clearly not related to a drug. But maybe if you took it back a few

more steps you would see that the drug is a [mmm hmm] more proximal cause and the pain is more of a distal outcome. [yeah]

S29: I mean, you could go both ways with pain, I agree sometimes it's clearly, but I, I guess I'm thinking of some of the newer drugs like Avastin which we know can cause bleeding and if it causes bleeding or some of these other drugs cause an infarct of the bowel because of the clot, or bleeding into an organ, then that certainly can cause pain. So I don't always think it's that clear-cut. [no]

(uncertainty)

M: Other people I have spoken to too have said it's pretty subjective and there's a lot of interpretation involved. And do you think that's because of the complexity of it? [yes] And what's your reason why?

S29: I think because there can be a component of the cancer and there can be a component of the treatment. [mmm hmm] And is it if they're on the drug have they had recent radiation you know, what are the other things that are going, are there other medications that they're on? So quite often I think it can be multi-factorial, it may not be just due to the one thing [yeah] so it's complex, pain is complex. So I don't think you can, sometimes it might be obvious, I mean if someone has bone mets and they come in and they have a fracture. That's pretty straightforward, it's their disease, but it may not always be that straightforward.

(very complex, a lot of variables to take into account)

M: Are you aware of any tools to help you in making these causality decisions?

S29: No. [no eh, you don't use any?] No, in fact I think people tend to lean towards putting it, like when they're not sure, and most people are never 100% sure, they'll say you know either probable or could be. **(err on the side of caution- method of coping with uncertainty)** And I think we see a lot of "could bes" more than any other category because people don't want to say, rule it out

100% that it's not. I mean the very straightforward ones, people will say it's most likely not, but if you're not sure people will often put could be you know. [yeah so more of a] There's a very grey zone and I think most people will tick off the grey zone. **(finds comfort in having a grey area)**

M: So the grey zone in the scale, is that what you mean when you say the grey zone?

S29: Yeah, because people it can either be, definite, you know what's the relationship to study drug, definite, um, very likely, unlikely or probable? So I think a lot of people will take the could be category, I can't remember the exact words but you know could be [possible] possible category because they don't know for sure. [yeah okay] Because there are so many things going on with these patients besides that one aspect of the care. [yeah, yeah] Now I think there are some definite things, like we know with some of the newer drugs like Iressa and Tarceva, a rash is common and diarrhea is common and so when you see those things if someone is admitted for diarrhea because they're on Tarceva then I think those are very straightforward. But I think we also, when you start putting these drugs out into the clinic that's when you start to see some things that might not have been quite so obvious in the studies.

M: Right, and why is that?

S29: Just because you're there, you're taking a drug that was used in a very specific population and you're giving that drug now to a broad, to a broader population that's not as highly selected. So I think that with any study drug, with any drug that goes from research into the clinic will often pick up on issues that weren't relevant or weren't obvious when they were in the study phase. [yeah] Yeah, that's pretty common. [yeah]

M: It's a smaller more select population. [that's right, that's right] Yeah.

S29: And then when you put it out to all broadly things start to come up, common things start to appear.

M: Especially if it's a rare event [mmm hmm] you just might not see it in such a small study. [that's right, that's right] It might only become apparent [when it's been used extensively] yeah.

M: Talking about that grey zone in the causality scale [mmm hmm] I'm just wondering if I could ask you to consider a scenario for me. Let's say you're treating a 65-year old female patient [mmm hmm] with a confirmed diagnosis of metastatic breast cancer. [mmm hmm] And she is in a Phase I clinical trial with an investigational drug [mmm hmm] and she experiences a pulmonary embolism. How would you assign causality to the study drug if there was a 75% chance that the adverse event was due to the study drug and a 25% chance it was due to all other factors. Keeping in mind this is a very hypothetical scenario and you don't know much about the study drug other than what I just told you. And the scale is certain, probable, possible or unlikely.

S29: That's a hard one and I think it depends on what your cutoff is and um, I think if someone told you that there is a 75% probability that it was due to the study drug I would probably put probable. I don't think I could put definite because it's not a 100% so I would probably put probable. [okay] **(subjectivity in cutoff ratios)**

M: And now what if there was a 50% chance it was due to the study drug and a 50% chance it was due to all other factors?

S29: Then I would go, what was the category below probable [possible] possible. [yeah, okay]

M: And what if there was a 20% chance it was due to the study drug and an 80% chance it was due to all other factors?

S29: Then I'd put unlikely.

M: Unlikely. [mmm hmm] So a 20% chance you would still say that was unlikely.

S29: What was the one above that, I can't remember? [possible]

M: And it's a 20% chance it's due to the study drug and an 80% chance it's due to all other factors. I'm not asking you to change it [no I know] I'm just trying to get a sense of where you're cutoff is between unlikely and possible.

S29: Yeah, 80 versus 20, yeah, I mean you could almost put in a less likely category in there, probable and unlikely. Sure it's still probable but the probability is now swaying towards the other arm. So I would almost like to say less likely rather than unlikely [yeah] which is not even a category. [so somewhere in between possible and unlikely?] Yeah, but you have no category for that. [laughter] So maybe I would put it then, I would probably put probable but qualify it as less likely which is kind of a [you mean possible?] yeah [but less on the possible side] yeah. In other words, there's sort of, yeah, I think you almost need, because you know, what if it's 20 versus 40? So you're still at less than 50% but 40% is a lot different than 20 [yeah]. And so 40% you could say it's still possible but at 20% it's possible, but less likely than 40%, yeah it gets difficult.

M: And of course we're never faced with these, we don't have these probabilities at the time when we're assigning causality. [right] But would you say you do prefer to have a scale rather than the yes related to the study drug or no not related to the study drug?

S29: Oh, definitely, yes, yes. [why is that] Because then I think you're going to get yes's for everything. If you just say yes or no, people unless they're absolutely 100% sure are always going to put yes, could be. And that doesn't really give you very much information [mmm hmm] because then you're going to get everyone saying yes except for the rare circumstances where it's obviously no. [yeah]

M: What are your concerns about how clinicians currently assign causality?

S29: Well we probably don't pay as much attention to it as we should. **(feels they do not pay enough attention to assigning causality)** I mean a lot of the initial information is prepared by the CRAs or the study nurses and I think in a practical everyday busy clinical environment we have these things coming across our desks to be signed almost on a daily basis. And I'm not sure if we think about it as much as we should, if we give it as much attention as we should, because it's just another thing to be signed. [mmm hmm, yeah] And there's been sort of very little attention paid to it in sort of the clinical research area.

M: What do you think the implications are with that?

S29: Well it means then that the information that the companies or the cooperative groups are getting is not going to be as accurate as they had hoped. **(feels lack of attention to causality assessment leads to inaccurate decisions)** I mean, what might be interesting is, even within the context of some of our meetings, like at the NCIC meeting if there was ever a workshop. It would be interesting to see, people would come and they could just give a few case scenarios and see how many people, like you have just done for me, rated those, and I bet you would get a very heterogeneous response [yeah] very heterogeneous. Well you'll be able to tell from these surveys as well, but I think people's understanding and their appreciation for the significance of it may be

there but I'm not sure if that's reflected in how people deal with these on a day-to-day basis. [okay]

M: Yeah, so that's, that a good idea, an NCIC workshop just getting people together and trying to understand how they are interpreting these.

S29: I think you could just sort of look at it as a CME type of workshop and put up a few scenarios and say look at the diversity and you know, that type of thing. I think any type of tool or anything that makes it easier for people would be appreciated.

M: What would make it easier for you?

S29: I think if you had those scales and you gave parameters to each scale you know [to each of the definitions [that's right, that's right]].

M: Can you give me an example of that sort of, I know it's tough.

S29: For instance you say 100% you know, and you can have what you mean by 100%, absolutely, no question, this is related to the study drug. And then probable, you know 80 to 100% likely related to the study drug type thing. You could sort of break it down into the different, you know, 0 to 20% you could say, for 0% obviously not at all related [yeah] and then you would have a category above that. Um, possibly related but less likely, you know sort of 5 to 20% and sort of categorize it like that.

M: So you think putting numerical ranges.

S29: That might help because if you have a brochure and it says, with this drug, the possibility of having this event is 20% and then you have that event or around that then you can say okay where does that fit into this scale? [yeah]

M: And they do that in the consent form don't they?

S29: Yeah, they do. In the consent form they always tell the patient's the less likely and then they give a percentage range and then they give the adverse event. [mmm hmm] So if we could have the percent and then the descriptor and a little description behind it that would give you the complete sort of categorization. [yeah] It still wouldn't be perfect but it would be, it might be helpful. [mmm hmm]

M: That's a good idea, others have mentioned that too actually.

M: What external pressures or influences have you felt from third parties when assigning causality?

S29: I don't really, because there's really no sort of, I can say having done a lot of pharmaceutical studies really there's not been a great deal of pressure. I have not felt pressure to say this is definitely or this is not. No they're pretty well hands off. [good, okay] (**Doesn't feel pressured by external sources when assigning causality**)

M: Now I'd just like to ask you if you wouldn't mind reading over these questions. This is an algorithm that was developed by a researcher named Naranjo. If you could just read over those questions and cross out any that you don't feel are relevant to the early Phase oncology clinical trial setting and then um.

S29: Some of these are very [very what?] was the adverse event confirmed by any objective evidence. Um, we usually if it's anything, an unusual adverse event it doesn't necessarily have to be confirmed by um [by objective evidence] yeah. So we have to rank the remaining questions.

M: Yeah, so now of the ones that are remaining, [oh okay] yeah if you could just rank them from most important to least important. So 1 is least important, 10 is most important.

S29: But there won't be, okay there won't be 10 but. [okay]

M: So you can just start and then work your way down, however you want to do it or work your way up from the bottom.

S29: This isn't easy to do actually. [I know, it's a tough task] Did the reaction appear when the placebo was given, but most Phase I studies don't have a placebo in them. [you can cross it out if you like] Unless it's going to be, I mean, this is specific to Phase I right?

M: Yeah, we're sort of, we're focusing on that to start. So if I only have [yeah, perfect] 1, 2, 3, 4, 5, 6. [super]

M: Now um, you crossed out 6, 7, 8 and 10. And so, what was your thinking of crossing out number 10 just that it's not necessary to have objective evidence?

S29: Well that's the only one I was thinking of, if anything I would put that 4, no I don't think you have to have objective evidence. [okay] Because an adverse event is an adverse event, you could have objective evidence but um, let me just try and think of a scenario.

M: It wouldn't necessarily affect your causality assessment though would it? [no] if you had it or not. [no]

S29: Like pain, pain is subjective, fatigue is subjective, I mean you can try and quantify it but if you think that the study, that the causality, that fatigue is due to the study drug you're not going to have objective evidence. [true] Weight loss,

well I guess if you have weight loss you can measure them in pounds but it's not always going to be there.

M: No, those are good examples okay. And then, why did you cross out number 8, was the reaction more severe when the dose was increased, or less severe when the dose was decreased?

S29: I don't think again that is going to affect causality, I think again if you have a reaction, first of all you may not have that, in a patient you may not have an increase in dose for a Phase I study. But I don't think that, you have to assess an adverse event at the time and usually you have to assign causality at the time and you don't wait until the next cycle um, if their dose is reduced or, or increased. Then essentially what you would be doing is backtracking and saying okay based on this cycle I'm going to go back and try to assign causality based on this backwards. So I think when we look at SAEs in these new drugs we look at the present and what's happening at that time. And we look at what's the event and what's the causality so you have an event and you have to say could it be or could it not be? [yeah] I wouldn't necessarily, if you're going to escalate or de-escalate the dose that would be another cycle and so that wouldn't necessarily influence how I assign causality on that cycle [at the time] mmm hmm.

M: And number 7 you crossed out was it detected in the blood in concentrations known to be toxic, what was your reasoning for that. Just again, you wouldn't have that at the time or.

S29: No, and I think again whether you have, you could have an SAE with normal non-toxic levels of the drug in your blood. So I don't think, that information is important to look at distribution of study drug and elimination of study drug. But again, as this is a Phase I you do not know if someone with normal blood levels for that drug will have an adverse event or not. It's not going to influence your causality. [okay, right]

M: What's toxic to one may not be toxic to another, is that what you mean?
[mmm hmm]

S29: For a given dose, for a given serum level in their blood. You could say someone could have an SAE with normal levels and someone could have no SAE with a toxic level in their blood.

M: So the two most important things to you were whether this was an expected event [mmm hmm] and whether um, you know, the timing [right] the time relationships. So did the adverse event reappear after the drug was re-administered? [mmm hmm] Okay, good, very good. What did you think of this?

S29: Um, it's somewhat, I think most people would struggle a little bit with picking what to put down and what to take out.

M: But if we were to modify this and say just leave the ones that you thought were most important [right] and kind of weight them according to how you think they should be weighted.

S29: I think it would be helpful, yeah. **(feels a tool would be helpful)**

M: Would you use something like this?

S29: I still think I would use something similar to what we talked about before. You know the um, and what would really help of course is if you have the information about the study drug and you have the toxicities and the likelihood of them occurring. And if you had then the event that occurred and that scale then you could sort of cross reference. So it's less likely this is going to be an adverse, you know, the expectation there's going to be a 20% chance of this adverse event occurring, this is the event that occurred and here are the scores and

here's the, the scale, then I think that would help. [yeah] Have them all sort of together. Which right now we never do, right now we get this piece of paper that comes to us from the clinical trials office and it says you know, it's in a little box and it says SAE, this is the event, tick off a box and that's it. [right, yeah]

M: Without really knowing what the probability of that event really is. [that's right]

S29: Unless you've had a lot of experience with the drug you know, but if you are in a Phase I study and you know, you may put three patients on it and that's it in your centre. [right] You don't have a broad experience with it. [no]

M: Now, I've done a few interviews and one of the things that's come out is that people have said that sometimes the communication is kind of poor among investigators in Phase I trials because you know, you only are dealing with one or two patients at your centre so it would be nice to have better communication. Would you agree with that?

S29: Yeah, I think that if you have just a few centers, some, one thing that might be helpful is if there was almost a site, an electronic site that you could access to sort of see what is happening in terms of adverse events with those patients at other sites. So that you, you know, because right now you're kind of in the dark when you're filling out those forms. [safety letters] You get the safety letters, that's true, problem is you get so many of them, some of them you look at very briefly. We get way too many safety, I mean we get, we get tons of them, we get piles this high every week from all the studies.

M: It's a bit unmanageable isn't it? [mmm hmm] So if they were summarized in a database that was accessible through your computers [mmm hmm] do you think that might be better?

S29: Because then you could access it at your leisure. [yeah]

M: And then lastly I'd just like to ask a little bit about your education in terms of the training you received, specifically with respect to assigning causality. How did you learn how to do it?

S29: Oh I think it's on the job training. [yeah] Um, I think most of us learn it through our experiences in the clinic. I mean I did have some time, I spent a year, did my fellowship at NCIC. Although you know, I really didn't, there was no specific component in my fellowship that dealt with assigning causality. I wrote protocols and learned about clinical trial design and methodology but not specifically causality. I've not really seen any specific courses or symposium, or CME events that have dealt with that. So I think that's, most people, most people really learn as they go through experience. [mmm hmm] **(no formal training)**

M: Do you think some additional education about assigning causality would be worthwhile?

S29: I think I mentioned this previously, something that would be interesting would be just a very short, you know, one hour event at something like a meeting at NCIC or you know, would be helpful. To make it in the context of a) being non-threatening b) not being boring, so make it a bit fun with some cases or some information and data. I think, they already do a new investigator training workshop at NCIC so it could become, it would be interesting to see if they could incorporate it into that workshop. [okay] But for the veterans, a little sort of a little CME update, that would be an interesting symposium.

M: Okay, that's great. Those are all the questions I have for you [okay] do you have any questions for me? [no] Any final comments or thoughts or?

S29: No, just whenever you know, the results of it are [yeah] I'd be interested in hearing the outcome.

M: Yeah, definitely, that's the idea, we're going to summarize all this interview data and put together a nice little executive summary [great] and send it out to all of the participants [great] and of course we'll keep you posted if anything more comes out of it. We're hoping to maybe present at the Fall NCIC meeting [okay] and if not then, then in the Spring. And then you know, we're going to start to develop our tool [right] and we might need to get your thoughts on that later [okay] if that's alright. [yeah, that's good] But yeah, thanks very much, I really appreciate your time, I know how busy you are.

Subject 30

M: So just to give you a little background about what it is that we're doing. I'm working with Dr. AA at the JCC and a few other investigators there, B is the manager of the clinical trials department. And I don't know if you're familiar with ML, he works for the Centre for Evaluations of Medicines at, it's through McMaster and St. Joseph's Hospital, he's a pharmacoepidemiologist. And so we've got a good group of researchers and I just joined on in March, I'm a Master's level trained epidemiologist. And so we're very interested in how investigators assign causality to adverse events that occur during early Phase, specifically Phase I oncology clinical trials. We understand that it's challenging, even for the most experienced clinicians. And that many groups expect prompt and sensible causality assessments. But that it's not always that straightforward and if it's done poorly there are definitely implications. So we're interested in developing a tool to help clinicians more efficiently and reliably assign causality to adverse events. And we feel that by better understanding your needs we can make the tool more relevant to you. So do you have any questions [no that's fine] before we start? Okay, great. And um, so first I guess, I'd just like to ask if you could recall a serious adverse event that occurred where you had to assign causality and it was fairly straightforward. Can you give me an example?

S30: Right, okay, somebody ah, was receiving cetuximab and had a, had a severe hypersensitivity reaction immediately during the infusion and it was attributed as definitely related. [okay, good]

M: And so it was that whole temporal relationship that led you to say it was definitely related?

S30: Temporal relation, known history of cetuximab causing hypersensitivity reactions, um, the absence of other probable or possible causes of that hypersensitivity reaction. It was a single-agent trial. [okay, that made it a little simpler?] There was nothing else that could have caused it. [okay] **(process of elimination)**

M: Now can you think back to a serious adverse event where assigning causality wasn't that straightforward? [um] Is there an example recently you can think of?

S30: Yes, okay, I can think of one. [can you tell me about it?] Okay, a patient was receiving an oral VEGF receptor antagonist and um, received ah, had been treated for about an 8-day period and had become very unwell while on treatment. We'd stopped the drugs and he had recovered, we dose-reduced him and gave him a single dose at the reduced level. And the patient within a hour had fever and chills, [mmm hmm] I can't remember all the details, I'd have to look at the chart. But had some, some possible urinary um findings on urine dip that suggested that there were, you know could have either been the drug or maybe this was just a coincidence and the patient actually had a urinary tract infection and had developed, developed urosepsis. So at the time of the event there was some uncertainty in my mind whether this could have been caused by infection, tumor fever or the drug itself. Because he had previously been been treated with the drug and he hadn't had fever and chills, but had been unwell, but not fevers and chills. So there was some uncertainty.

M: When you said he was unwell after being treated for 8 days, what do you mean?

S30: Fatigue and even some mild cognitive difficulties um, grade 3 weakness, anorexia, some nausea, um, a variety of symptoms. [okay, alright]

M: So what led you to, how did you assign causality in that case?

S30: Well in that case I felt that the event was ah, I'll have to see actually how I graded it, but I believe I said it was, it was probably related but I wasn't absolutely certain given that there were, there were other possible causes. **(it is hard to be certain even with very slim possibilities of other causes)** So if you have another possible cause or at least at that point, at the point where it was attributed we felt there were other possible causes. So I didn't want to say it was definitely related um, and ah, but temporally it was associated with it and the patient had been unwell on the same drug before. So there was, there were enough um, both temporal and ah, and previous experience with this patient, reasons why we believe that it might have been related. However, in terms of experience with the drug, it's a relatively new drug and um, hypersensitivity reactions, it's an oral drug, had not particularly been described. **(strong emphasis on temporal relations)** Um, so there wasn't a lot of data to go on in terms of, in terms of background data for the drug with this particular event. [mmm hmm] so there remained some uncertainty from that point of view. And also there was no, there was no um, biologic, particular biologic reason why this drug might cause um, in terms of mechanism of action. So we didn't know any mechanism of action why a patient might develop fevers and chills with this drug. So, some uncertainty and it was, it was, you know there was some debate between possibly related versus probably related and I said probably related. **(debate between causality scale measures seems to be quite common)**

M: That seems to be the difficulty determining, whether it's possibly or probably, and how do you differentiate.

S30: Well in the end it doesn't matter because these things are all dichotomized generally in trials. If it's possible, probable or definite it's considered to be attributed to the drug and it's unlikely or definitely not attributed, or definitely not attributed then it's considered no. So when you look at how, how these things that are eventually graded, anything that's possibly, probably or definitely related is still attributed to the drug [mmm hmm] for the purposes of these studies. So in some ways possible versus probable doesn't matter, it's more important the definition of possible versus unlikely [mmm hmm], that's, that's really where the, the, it's important that the correct, the correct side of the fence is chosen as much as can be done. [okay] **(greater standardization of causality scale measures is needed and regarded as highly important)**

M: And how do you differentiate between possible or unlikely? Do you have sort of a?

S30: Well again, you use all of the factors, you use whether this is the first event, or whether this has repeatedly happened in this particular patient, so the individual patient experience. You use the information from the investigator brochure and information that you are receiving in an ongoing mechanism, feedback from other patients that are receiving the drug. **(new idea- using feedback from other patients to assign causality- although probably self implied)** You look at the biology of the drug and say are there, are there probable causes, are there theoretical reasons why the drug would cause this particular side effect. So you know, if you're looking a drug that affects the VEGF system and they get hypertension well there is, there's a good theoretical reason why that would be the case, or wound healing problems. So if you know the biology of the, the mechanism of the drug you can look for associations for that reason. And then there's the temporal association [mmm hmm] and um, I'm sure

I'm forgetting something. **(forgets some components of causality attributions- may suggest that a tool would be a helpful reminder)**

M: So are there some general guidelines that you tend to follow then to say ok well I'm going to say possible this time or no I'm going to say unlikely this time?

S30: Well I think in the early development of a drug if there are other, if there are other, let's say the very first few patients that are being treated with the drug. Um, if there are other reasonable causes then I'm not overly quick to attribute them to the drug. Because I think you can falsely label a drug with all sorts of um, toxicities that have nothing to do with it. So if I'm treating patients with colorectal cancer and they elevate, there's a little bit of elevation of liver enzymes um, then, and we know the patient has liver metastasis then I'm not quick to say this, this is attributed to the drug. My leaning in that case would be unlikely because we know that patients with colorectal cancer develop elevations of their liver enzymes whether you do nothing to them or treat them with any treatment. So if, if there's another probable explanation then I'm going to say unlikely. If there's no other probable explanation [mmm hmm] there are only possible explanations. So some, a patient develops um, low platelets and there's no, you know slightly low platelets and there's no other obvious cause, there's no other probable cause [mmm hmm] outside of the study drug then I'm more likely to say possible. Or if there is, even if there's no track record I'd say possible, if there is any track record at all of thrombocytopenia I would more likely say possible, you know probable or definite. Again depending on temporal association and if it's the first time it's happened. [all those factors okay] So it's really, it's, there's, it's a combination of factors when you're making decisions, when you're designating causality. **(multiple factors make the decision making process very complex; they err on the side of caution by attributing the toxicity to the drug, in instances when they are uncertain)**

M: So that's sort of a less conservative approach really, um, erring on the side of, sort of protecting the drug I guess right?

S30: Well um, it's, I don't know it's less conservative, I don't think it's right to say that every bad thing that happens to a patient, every abnormal blood parameter, every um, you know, every time the patient gets a cold or whatever that it could be attributed to the drug. I don't think that would be right, I don't think that would be right or fair for the development of the drug. Um, so again, it's, I don't think it's conservative or liberal [mmm hmm] or whatever, it's a question, I think it has to be a balanced approach [yeah] every time you make an attribution. **(tries to be balanced, unbiased when making an attribution)** Particularly in the early development of a drug it's important that those are as accurate as possible. And sometimes you'll make mistakes, sometimes you'll have, the first time a toxicity comes up you say, well how could that be related you know, or could that be related? And you might, you might say possible or you might say unlikely. And then when the third patient develops the same symptom which you thought could be from some other cause, you say wait a minute there's a pattern developing here. From now on I'm going to put all these as probable or definite so I think that's where the advantage of seeing many patients on the same trial. I think the danger when you have, when you have a trial with 40 centimeters, 40 centres involved and all of them put on two or three patients that nobody has an opportunity except for maybe the people at the central office. Nobody has the opportunity to recognize those patterns. So it's better to have a centre and put 10 or 12 patients on, on a Phase I study or an early Phase II study [yeah] to be able to identify what these, what these patterns are. **(hard to find a balance between the safety of patients in early phase clinical trials and the number of patients you can recruit- the more patients the easier causality attribution is)**

M: So that would certainly make it easier for assigning causality then is having more patients [per centre yeah] per centre. Is there anything else that would make assigning causality easier?

S30: Um, well, you can imagine, you have the investigator brochures and you have databases from drug companies. But it would, you know, in this modern day of computer technology it would be nice to be able to type in, type in a toxicity for a particular drug you know, it would have to be obviously a secured database. But if drug companies would make available these databases, you could type in a toxicity and get an instant idea of how many other patients had this toxicity regardless of whether other investigators felt it was associated or not and it might give you some idea whether this was an unexpected percentage or an expected percentage in a population. [right] So that, that kind of information could be helpful. I suppose drug companies could make that available although they may be reluctant to do so. [yeah] **(feels disconnect with other trial sites)**

M: But you do receive those safety letters, the CIOMS reports right. [mmm hmm]

S30: An overwhelming number of them yeah.

M: So in the form that you're receiving them now it's not a very useful tool.

S30: Unless you can retain, like I must receive, I don't know, 30 a week for different drugs and you look at them but ah, to know the, you don't know the denominator right. When you find out that Oxaliplatin has caused, I don't know, whatever, some eye problem or something like that, has been reported may be to cause some eye problem. Um, how do you know that that's one in a million or one in a hundred or one in ten thousand? Like how many, how many events does this represent, is this a pattern, is this just a one-time thing? [yeah] So these, this kind of data, those reports are helpful in that you know, it, it twigs your memory and imagination and you put it into your database but is it, is it accurate

enough to help you with attributions? Not necessarily. [mmm hmm] Obviously if important things come up, they are supposed to be put into the, not just come up on adverse event reports. But they're supposed to eventually come in through amendments into the consent forms and at least that is a standing record of existing reported attributable toxicities. [right] So that's an important, obviously another important source for. [the consent form] The consent form, I mean the consent form documents everything that's been reported as attributable to the drug.

M: Are you aware of any decision-making tools to help you in attributing causality?

S30: No, and I would be hard pressed to imagine that, well there are in many protocols, there are rules for attributions of, of toxicities so I guess those are tools.

M: What are the, so they actually

S30: They'll talk about, yeah, in some protocols they'll talk about when, when it's to be attributed and not. Can't say I've seen it in a protocol recently but I know I have seen it in protocols before, they talk about under what circumstances things should be attributable.

M: And is that helpful? [yeah, sure] Is there anything else you can think of that would make assigning causality easier?

S30: No [no okay]

M: Do you have any concerns about the way causality is currently being assigned?

S30: Well again, if you're only seeing a very small number of patients it's difficult to recognize patterns. Um, and it can go both ways, if you only see a very small number of patients you may underestimate or under-relate particular symptoms to, to the drug. And the same thing can also happen where if, if you just decide that every bad thing that happens to a patient is going to be possibly attributable then, then not only do you jeopardize the development of a drug but you also, those things all get added to patient consent forms and they muddy the waters for patients. Patients should be, shouldn't be told all of these possible things that can happen if indeed most of these things were in fact related to their underlying diseases. So I think it's misinformation for patients as well as for, as well as for development of the drug. So it's, you know, it's not just a question of patient safety, it's also a question of, of adequately informing patients and not clouding their perception of an agent. [okay] **(feels patients are ill-informed)**

M: What external influences or pressures have you found or felt when assigning causality?

S30: Well with smaller drug companies you tend to get more queries about why did you assign this as attributed or not attributed? You know, what do you think the underlying pathophysiology is? and so you know, smaller drug companies particularly when their entire livelihood depends on, on a single agent will, will be, will, I don't know if pressure is the right word but they will definitely discuss extensively how and why you've chosen that something is related. **(feels more pressure is felt by smaller drug companies)** Typically if I have something that I, if I see that there may be a pattern emerging and I've started attributing a particular event to a drug. I also start doing extra safety checks, or extra evaluations of that, or looking more careful in individual or subsequent patients that I treat and in that particular patient to see if we can find temporal associations etc. So again, seeing several patients can be helpful in, in evaluating and identifying um. I have an example of, I saw thrombocytopenia in a patient on a new drug and it had not been reported and it was not in the consent

form. And on re-challenging the patient I made sure that we checked the platelets a little more frequently and indeed it happened again and it happened a third time. And we checked it in several of our other patients and it was happening in several of our patients so we were able to identify based on volume of patients and careful evaluation that ah, that the drug did indeed cause this toxicity. And whereas others hadn't reported it at that point [good for you] so it happens. [okay]

M: I saw you looking at your watch, you've got to go.

S30: Well soon. [yeah]

M: The last thing I would like you to do then is if you wouldn't mind reading over this algorithm. The questions were developed by a researcher named Naranjo. If you could just cross out any that you don't feel are relevant to the early Phase I oncology clinical trial setting.

S30: That are not relevant. [no] Are there previous conclusive reports on this reaction? Did the adverse event appear after the suspected drug was administered? Did the adverse reaction improve when the drug was discontinued. Did the adverse reaction reappear when the drug was re-administered? Are there alternative causes? Did the reaction reappear when a placebo? Well we don't do that [alright cross it out] so cross it out? I mean yes, I suppose that would be, that would be interesting information but it's not practically important in a Phase I study. Was the drug detected in the blood in concentrations known to be toxic? Well I suppose that would be relevant if one had the information. Was the reaction more severe when the dose was increased? So dose relationship yes, although we don't usually know that in single patients, although there can be inter-patient dose escalation. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? That's, sure. Was the adverse event confirmed by any objective evidence? Okay [okay] sure, those all look reasonable to me.

M: Okay, now could you rank them in order of importance, so 10 would be most important and 1 would be least important. Well I guess you would have 9, so 9 would be most important and 1 would be least important.

S30: I should say the placebo, this is an issue for Phase III obviously. [mmm hmm] Like if you see the same incidence of a toxicity in the placebo arm as you do in the treatment arm, that suggests that if anybody was attributed to the drug they probably were wrong. Okay, so what are the most important, this is, this is just, I don't think there's a right or wrong answer here but um. Well I think recurrence on re-administration is very important, so that's a big one. Temporal association is pretty key, if it happened beforehand then, I mean these are all important. Did the adverse reaction improve when the drug was discontinued, that's also important. That's less important. Was the reaction more severe, that's somewhat important, previous reports is important, reasonably, alternative causes is important. Um, previous similar reaction to the same drug, that's the same thing as it occurred with re-administration, these are both the same, to a large extent, the same question. Did the patient have a similar reaction to the same or similar drugs? Did the reaction reappear when the drug was re-administered? This is the same. Was the adverse event confirmed by any objective evidence, somewhat important. So the number one, well it had to occur after, I think that's got to be number one, if it occurred before then it was not.

M: Oh, you mean 10 is most important.

S30: Oh, 10 is most important? [yeah] 10 okay. So yeah, sorry I should look at your scale here. So yeah, the temporal is key. Recurrence with repeated administration is also very important, if you have that information, you don't always have that but if it happens repeatedly after each dose that's important. Oh I can't write, okay I'll go to 8 here, and then this will be 7 [beeper goes off]. The side effect disappearing obviously that can't always happen, it depends on what,

you know, sometimes side effects can take time to resolve [right] if there's inflammation. So that's important but, but not as important so I'm going to say this is, I'm going to say this is, 6, I don't know maybe that should be 7. And this is going to be 5, this is going to be 4. Yeah, in a Phase I study this is important but in a single patient this is less of an issue [what's that number what?] number 8. So number 8 says was the reaction more severe when the dose was increased?, a dose response curve is very important but in a single patient you often don't have, you're not going to be treating a single patient with multiple doses. [right] So if you've seen 10 patients and you notice that at dose level 4 there is more of a particular thing that is very helpful, so it's not unimportant but it's. And then this would be 2 I guess, was the drug detected in the blood at a toxic level?, that's important, but less important maybe. [alright, great]

M: I know that was a tricky exercise, thank you. It's a, yeah, it's tough. What did you think of this? Do you think if we were to sort of modify this based on what you've suggested here based on.

S30: Well this is exactly that you, this is exactly the kind of thing that I've seen written into, into protocols. You know, just temporal association, dose response, you know all of these issues, temporal association, dose response, recurrence with re-administration, resolution when the drug is discontinued. These are all, these are all things that are important and ah.

M: So do you think that if we were to, you know, do you think this would be a helpful tool in assigning causality if we were to [to] encourage people to think these things through before they.

S30: Again, there's, there are many factors here and um, um, and when you're looking at alternative causes, that's generally where it comes down to an uncertainty. It's not the temporal association it's not the, it's not, when you're doing it for the first time like the first cycle with a patient it's not a question of how

many cycles have you given and has it come back repeatedly after? After it's come back repeatedly it becomes a lot less of an issue, you know it's related. But it's really, when you're giving a drug to a patient for the first time it's looking at all the existing factors. Um, the patient's underlying condition, other things that might have been causing it and that's where, that's where there's uncertainty as whether it should be unlikely or possibly related. So that's, my guess is that most people are familiar with these um sort of rules for causation [yeah] I would guess. **(assumes everyone follows the same procedures for assigning causality)**

M: Well thank you, I really appreciate the time you took to spend with me today, I know how busy you are.

Subject 31

mentioned even the most experienced clinicians find assigning causality to adverse events challenging. But many groups such as industry sponsors, clinical trial cooperative groups and research ethics boards they all expect prompt and sensible causality assessments. But it's not always that straightforward and if done poorly it can have implications. So we're interested in developing a tool to help in efficiently and reliably assigning causality during Phase I oncology clinical trials in particular. And we feel that by better understanding your needs we can make this tool more relevant to you. So do you have any questions before we start? [no] Okay, great. So, I guess, I'd just like to start by asking you if you can recall a serious adverse event that was fairly easy to attribute the causality to, can you think of an example?

S31: Well with chemotherapy, nausea and vomiting are pretty well, you do know that is related to chemotherapy. And I think most of us are in the practice of reading our protocols and even the patient consent that states that side effects that are more likely, less likely and rare. So that if a patient experiences them then you, you can either refer back to the protocol or you remember reading that yes, that is a side effect of your therapy. Like, for example, taxanes we know that peripheral neuropathy, and bony pain or myalgias and arthralgias are, if they

start to experience something like that, it is the taxane that is causing that. So I guess being familiar with the side effects of the chemotherapy you're giving is really important so that if the patient experiences them you can go back and say we know for sure that, that is. Another thing is to establish a baseline with your patient, so if they've had a back injury and they experience lower back pain before they even start chemotherapy. And then they say to you well I have lower back pain but it's the same as it always has been. Well then you say well it's not related to your chemotherapy then because it's the same pain that was happening before. So I think it's important to know your patients from a baseline perspective and asking baseline toxicities that are relevant to your particular therapy or your Phase I study tools. So that you know whether or not it's attributed or if the patient had this prior to then you know it would not be related so. [mmm hmm] We commonly, or I commonly use the CTCAE version 3, some studies I still use version 2. And I like the way those are set up because I can keep in my mind when the patient's explaining the severity, then I can say well I've had slight nausea on day 3 to day 7 and my appetite was kind of lousy those days so I think okay that was a 1 and that was a 1. If it's nausea you know, where I couldn't eat for a couple of days and you know the severity is increasing because of the amount of impact it's having. So having a grading scale that puts into perspective, well it has, it's present but it's not affecting their activities of daily living or they're not requiring medication then you know sort of. So those things really help because if you get to a grade 3 and you need analgesia or if you get to a grade 3 and they're needing intravenous parental support then oh yeah, that's where they're at then you know exactly what grade they're at. If it's not to that point but it's more severe and affecting their appetite and ability to eat then you know it's a 2. So, ques like that really help [mmm hmm] to put into perspective just what grade you're at. And it's also important because if you need a dose reduction based on a toxicity level then you're making the right, the right assessment. [right]

M: Now can you think back to a patient that had an SAE and assigning causality wasn't that straightforward, can you give me an example?

S31: Um, yes, I had a patient who ah, developed a pulmonary embolism and we couldn't say for certain it was the chemotherapy she was on. It could have been disease related, it could have been disease progression. There was a number of issues but we weren't clear um, and yeah, we weren't able to assign. So the study gave us the option of probably or possibly and you know, or could be. So that's where we ended up, we weren't able to definitely say that it was related. [mmm hmm] Now they always ask, they always continue to ask for clarification after that to try and establish if it definitely is or definitely wasn't. **(pressure mainly lie on possible and probable decision outcomes, not so much related or not)** But um, the patient passed away so we didn't, we didn't have resolution, except death was our resolution. Sometimes I think that is a way to eventually, as it progresses and as it resolves you can sort of maybe after the fact like retrospectively say like well yeah it probably was or it was definitely. So sometimes there are grey areas and at the time it might be difficult but retrospectively by continuing to look at data after the fact then you're able to um, to decide at a later date.

M: So when you say it's grey, what do you mean exactly?

S31: Well that you're not, you have your treatment but you're not sure that this is definitely related to their treatment and it may be related to other, like it might be disease progression or the nature of the disease. Or maybe the patient becomes more inactive because they're fatigued or anemic from chemotherapy. Like, there's other issues that could cause a pulmonary embolism and it's not directly a side effect of the medication but secondarily to. [mmm hmm] So then it's, it's well it's not directly the medication it's, you know, medication may have caused this, it may have caused this and as a result here we are but. So then it's, you can't really say it's definitely related. [yeah, okay, good]

M: So that patient who experienced a pulmonary embolism was that patient on a trial? [yes she was] and was she, what kind of cancer did she have?

S31: She had brain cancer and she had metastatic disease to liver and bone and later brain, but she never had pulmonary disease. So that's, I think you know it's, I mean, I remember speaking to the physician and he said I can't say this is directly related. I mean if the patient received chemotherapy and develops a rash with 5 minutes of infusion you know, because that's tangible that that's, because something is going in and the body is not agreeing. It's tangible evidence that there is a toxicity. But something that is not a direct result but could subsequently happen is I think a grey area, and it could probably, it might have been, we don't know for sure. [yeah] So that's why I say it's kind of a grey [yeah] a grey area. [yeah] **(takes comfort in accepting a grey area of causality)** But she was on a clinical trial and they did request, subsequent to even her, her death, any other information that could have been brought forward to help them. And I think it was decided at the end that it wasn't certain what the causality was so. Sometimes I think they end up being grey [yeah] there's no definite causality relation so. [yeah]

M: Are you aware of any tools to help you in making that decision a bit easier?

S31: Um, [you mentioned the CTCAE] yeah, but again with that, is it present, or is the patient on um, anticoagulant therapy, are they on oxygen therapy? But it assigns a grading for toxicity but not causality, so no there really is not. Again, if I were to look to my protocol and it was maybe even a rare side effect but it wasn't one of the ones listed. [mmm hmm] So again, we thought well it's always possible this could be the one out of a thousand that experiences this as toxicity but um. Yeah it would be difficult to figure out what tool would be, I mean that's sort of a very extreme I think. I think you're probably looking at more common issues to assign causality. So I'm not sure what tool would be handy, I mean

because we do have you know, the companies do provide us with the list of common side effects but um. [in the protocol?] Yes, and in our investigator brochures and product monograph and things like that. So we have some tools in place, I mean sometimes it is time consuming to go back and look through product monographs, read through pages and pages of very complicated information and also chemistry associated with it but. **(feels time pressures)** Um, so maybe simplifying something like that would be useful because it's, I mean, I admit I don't often read my product monographs and my investigator brochures because there's so much literature in there and I just don't have time to wade through. [yeah] So maybe a more simplified version of something like that, this is the drug, this is how it's been used, these are the common side effects. And then you could have a quick reference, oh yeah, this is something we see all the time with gemcitabine or whatever the agent is. [yeah, okay]

M: Are there any general guidelines that you follow when you're assigning causality?

S31: Um, again with seeing patients on a particular study and using drugs that you've um, experienced in the past. Or you know, you've spoken to patients in the past and they're all, there are always common side effects that you know are common to these drugs. So I guess with experience you know again, if a patient is having peripheral neuropathy that it is the taxane, that is one of the issues with a taxane. So it's very, not easy, but it's almost you know, this is, it's fairly black and white that you know, if you look it up that is a common side effect. As is you know, musculoskeletal pain. So the more you hear patients experiencing those when you get to the taxane then the more you realize that yeah this is, it is, the causality is definitely there. Um, so other than that, I can't think of a particular guideline that, I guess, and again knowing your patient's baseline, is this something new for them? If they haven't experienced it before and they're on new agents then, then it leads you to believe that the causality probably would be the new agents you know. Like I said if they had runny nose and teary eyes prior

because of allergies then if they experience them after, then it's probably not your agents that are causing them but it's probably the patient had a pre-existing condition. Then you would know, well it's probably not the agents that we're using then. So to establish a baseline again but you know, I mean if they had hot flashes before and we're giving them a taxane that's going to cause them, well they had them before [yeah] so you know, maybe not and it's just them, and their condition. [yeah, okay]

M: What would you say are some of the problems or challenges when assigning causality?

S31: Um, I think while they are on active treatment it's much simpler because as they are experiencing, as the agents go in and create more side effects it's easier to relate causality. When toxicities linger into the follow-up phase and they go onto, for example our breast patients will go onto a hormone. Chemotherapy agents will cause for them hot flashes sometimes if they are putting women that are close to menopause they will begin to experience symptoms of menopause. Then you put them on a hormone which also causes hot flashes and bony pain and is it left over from our chemo or is it something attributing to the hormone that we are now giving? And when does one end and the other begin? Because we haven't really given a fair amount of time in between. So I find sometimes I can't really say this is chemo anymore. Is it the tamoxifen or gee wiz is this the chemo still and we're adding to that effect with an agent that also causes hot flashes and the tamoxifen is also? You know, so that for me is like when do I say 'no, it's six months and it probably can't be chemo anymore'? There is no guideline to say you know, it should be out of their system at this certain time and if they experience these side effects or toxicities, it's probably, the causality is probably something else now because after this length of time it can't be your chemotherapy agents any more if they've been on them for say six months or a year. Or when is it, when is it finite that we can no longer say, we can no longer assign causality? That, that for me is a struggle.

M: Yeah, I would say that certainly makes it, and have you had an example for me, can you?

S31: Often, often. [yeah] Because these ladies, for example on a study I have right now, they have between 3 and 5 weeks to go onto a hormone when they finish their last dose of chemotherapy, they're also receiving radiation. Well all of those agents will cause fatigue, radiation can cause fatigue, hormones can cause fatigue and chemotherapy agents you know, can cause fatigue. I mean secondary to anemia or you know, if their white cells are dropping or for whatever reason. [mmm hmm] So when they're continued to be fatigued post-chemo, excuse me, but then you look and see oh they're receiving radiation treatments every day for 5 weeks and no wonder they're tired. Well which is, where is the causality, is it both, is it no longer chemo but now it's radiation? So often I struggle with, with when to say it's one treatment versus the other that's, that I should assign causality to. [yeah] I don't know how we would, how we would get around that. Maybe there is a guideline you know that says most people at the end of this period of time should have metabolized these agents and should no longer be experiencing these effects. So causality is probably not, you know, not with this agent so look at what else is going on so, maybe something like that would be helpful. **(they do not feel as through they have adequate resources to make the most informed decision they can)**

M: Yeah, so like guidelines with respect to [maybe timelines] yeah, elimination of the drug. [mmm hmm] Okay.

M: What are your concerns about how causality is currently being assigned?

S31: Well for example when you have three different treatments that could possibly, then is it accurate? You're assigning causality to an agent that may not be responsible, it maybe left over chemo toxicity and then you're saying well

perhaps it's tamoxifen. Maybe it's not the tamoxifen maybe it's the fact that the patient is coming in every day for 5 weeks to receive radiation and they're worn out from that. [yeah] So you may not be accurately assigning causality in that instance. So um, you know when they, I don't know if it impacts marketing they're having to state that fatigue is an issue when perhaps it's not. **(feels concerned about the impact of their attributions)** So I wonder about the accuracy of assigning causality when there's multiple agents involved, or multiple therapies involved and they may share common toxicities. [mmm hmm]

M: So you said you worry about the marketing, what do you mean?

S31: Well I, you know if they're looking at patients in long term and saying, well you can have fatigue for up to 2 years after chemotherapy. So when they put out the, the common um, toxicities, less common and rare, would that be in there? Because a lot of these women are experiencing these toxicities. But yet, causality may not be, may not have been an issue with the particular agent but it's there, we said well yes they're still having, this um, toxicity and perhaps it's this agent. So you're assigning causation when maybe it's not it may be something else. So as a company I think they're obligated to list that as a part of their um, their package. Maybe not, maybe they don't take into account certain timeframes. **(disconnect from company sponsors)** Maybe they have a tool. [laughter]

M: Okay, do you have any other concerns, about how it's being assigned?

S31: Um, I think with experience you get better at knowing what regimes and what therapies cause, what are common to certain things so that you're more comfortable saying you know, if you're on this chemotherapy and you're having nausea and vomiting we're pretty certain it's the chemotherapy. So you get more confident saying yes, it's definitely related. Um, there are still some grey areas where I say well it could possibly be, I'm not really sure but I'm saying it's possible. So I guess, yeah, that comes with experience and you know, talking to

patients, doing our interviews with them through each cycle and, and you get more comfortable saying to them you know, 'don't worry you're not falling apart, that's your chemotherapy that's causing all that, so once you're done it will get better. And yes that is what's causing you to feel this way now but you know, later on it will subside as you excrete all that agent'. So use your confidence to reassure your patients that it is, the cause is there now but it will. So that's experience I guess as I get you know, better at it. [right] I definitely, when I was new, definitely it was a struggle to decide but again I know now if I know my patient's baseline and I know what's common to this regime then I can safely say this, this is probably, not probably. **(a get a sense that they have a strong connection with their patients, they care deeply about their safety and outcome of the trial)** This is your chemo, remember you said you had a back problem prior to chemo?, so it's probably your back. Because we're making you lie for five hours to receive your treatment and you know, that type of thing so. [yeah]

M: Now you said you've been here for a year in this position. [yeah, a year in April] How did you learn how to assign causality at the start? You said it was pretty hard, did you have any training?

S31: No. [no]

M: So how did you figure it out?

S31: Well we have our tools, the CTCAE, versions 2 and 3. Again, making sure that, I would look back and know my patient's baseline. Reading the protocol and the patient consent that the patient gets that explains what are common toxicities. And you know, referring back to that, you know, certain things they are experiencing are definitely related and the cause is definitely this regime. [mmm hmm] So using the tools, so yes if we had more tools it definitely would make life

easier. **(feels tools would be beneficial)** Um, I guess with this job, a lot of it is just on the job training, you learn as you go. [okay]

M: A lot of people have said that, that there really isn't much training out there and that's kind of surprising. [it's scary isn't it?] What additional education about assigning causality do you feel needs to be made available? Because you're fairly new to this [yeah] so can you think about what might have helped you a year ago when you were starting?

S31: Um, I don't know, I mean, a lot of the agents we give, even in breast, there are so many different agents and so many, I mean they do have their unique issues that are definitely a cause of their, their regime. So um, I mean right now we go to in-services whenever we can, that the drug companies often, they will offer them and we go and they talk about their new, their new therapies and what. They'll talk about what they're designed to do and what the side effects are. So that when you get involved with a lot of these new therapies you remember what the sort of common issues are so that you can assign causality. **(can feel deeply involved with agents)**

M: Do you mean like the investigator meetings?

S31: Yes and in-services that companies come to and they will talk about specific agents. Like we have a lot of that on um, anemia and talking about what anemia is, chemotherapy induced anemia, when to treat it, what sort of are common um, issues with anemia. And then the drugs we can use and what the side effects of those are. So it's like a package and you have all your information with everything involved so going to those has helped. But um, I'm, I'm not really sure, I mean what?

M: Do you think, I guess, you know, others have said maybe sort of a workshop or um.

S31: But do you do a general presentation as to

M: Well, what would you like? If you had your, if it was up to you [mmm hmm] what would work best for you just starting out?

S31: I guess, I guess it would have to be general initially because after that you do work with specific agents and but is it, you're talking specifically about not what the toxicities are but how you decide whether or not it's your agent [yeah] that's related or if it's not. [mmm hmm] So yeah, a general workshop that would definitely say here's some of the tips that may help you to decide, you know, remember to use the criteria or guidelines that are associated with your protocol to help you to decide whether or not these are. And how to grade them because that's always important. Um, yeah actually it would have been very helpful to have a workshop. And then probably hands on, like you're given an exercise where you have, and you know, we've done that before and those really help. You know, you have a scenario and you're given a worksheet and you have to decide you know, how do you, is this related or is this not related? [yeah] Yeah, definitely, that probably would have been, even just to, because it would be general, even just to be an eye opener or even just um, open the mind to this is what you're getting into and this is what you're going to have to do and you will have to decide, you know, to assign causality and to grade it and yeah, yeah it would have been helpful. [laughter] [okay, great]

M: One of the things that, oh I know what I wanted to ask you, have you ever felt any external influences or pressures from third parties when assigning causality?

S31: No, I can't say I have. Often I will confer with the physician because we interview the patients and then the physicians interview the patients. Um, sometimes I, I really prefer when we do it together because we both hear the same story. **(feels there are benefits to assigning causality as a team)** And

sometimes the patients will tell the physicians one version and then we'll get either a more detailed or a less detailed. Or there will be some components missing. But often if I am not sure I will go to the physician and say did she tell you about that um, um, back pain that she had and she had to take Tylenol #3 before she had some relief? And what do you think? Do you think it's related or um? Actually I had a situation recently where a patient received Eprex and yet I was certain it was the agent, it was the first time that she received the gemcitabine. And one of the common side effects of gemcitabine is a rash, and she developed a rash, a grade 3 rash which is quite severe. And um, um, there were two physicians involved, one that had seen her with the physician being away and then he came back and saw her. And he admitted to me that he believed it was the gemcitabine but she, the initial physician thought it was the Eprex because it was the first time for both agents. [right] So they stopped the Eprex even though the patient was anemic and did not offer any other support. And um, just added other agents to help buffer the effects from the gemcitabine and the patient did not have any further rashes but sort of had to continue with an anemia that was you know, causing her some, some issues with her quality of life. [right] It would have been nice if we could have established causality unanimously but. [yeah] **(further exemplifies the need for a standardized approach)** So I say going to the physician but if there is more than one involved there can be more than one opinion. [yes, okay] But generally getting a consensus is helpful if you can go to your physicians and they often are very good at saying well. Even when I don't think it is, they'll say no I think it was you know, the agent that caused this, this is definitely associated and yes we'll say it's, we'll assign causality to that. So I don't try to decide on my own, if I'm not sure I will go and ask [yeah] for other input and then we'll try to make a decision. And then we'll all have the same version, the same story. [yeah]

M: What I'd like to do now, I'd just like to ask you if you wouldn't mind reading over the following questions. This was an algorithm that was designed by a researcher named Nar, Naranjo. Sorry getting all tongue-tied. If you could cross

out any questions that you feel are not relevant to the Phase I oncology clinical trial setting [mmm hmm] we can start with that, that would be great. [okay]

S31: I don't know, I haven't done Phase I [okay] so I'm not that familiar or comfortable with Phase I, but I um, from reading I think that Phase I is to establish reactions in the patient that has been used in a clinical setting and they want to see how patients react. [yes, yeah] Okay

M: Primarily to look at the safety of the drug. [okay]

S31: Okay, so there probably wouldn't have been previous conclusive report on a reaction. So just cross them out. [yeah] Did it appear after the suspected drug was administered? I think all of these would be important [okay] except for I don't know how much previous. Although this is something I use a lot is looking back and see what's previously stated. [yeah] But in Phase I you probably wouldn't have a lot of [yeah] conclusive reports.

M: Yeah, you would have an IB but it probably wouldn't be as comprehensive as say in a Phase III trial. [mmm hmm] So now with the remaining ones could you just rank them in order of importance? So you know, 10 would be most important [okay] and 1 would be, well I guess you could start from 10 and work your way down. [so just number them] Yeah, you could just write beside them [oh on here] yeah, just whatever rank you want to give them.

S31: Was the adverse event confirmed by any objective evidence? [is that confusing?] Well objective, are we able to tell, I mean is it objective, I mean when a patient tells you it's, hmm. Okay, I don't know.

M: It's a difficult exercise, but I guess we just want to get a sense of you know what people feel are the most important issues [okay] most important factors when attributing causality, in assigning causality. So least important was, was the

drug detected in the blood in concentrations known to be toxic, why did you rate that one so low?

S31: I don't know, it was just sort of from what numbers I had left to assign [laughter] I did find it difficult. I mean every one of those would be really important issues. If I could I would probably give them all a 10. So I found that even something that's a 2, well I think that could be a 10 if you look at well, is there something else that you could assign causality to, that would probably be quite high. And again, if you did blood work and saw that maybe the dose you are giving is too high and if you lower the dose it would still be effective but not have as much side effect, that could also be a 10. So I found it difficult, so it was basically what numbers do I have left to assign. [yeah] They would probably all be, if I could I would give, they would all be important. [okay, good]

M: What did you think of this as a tool if we were to you know, if we were to remove this question and weight them accordingly and then somehow link that to a causality assessment. Do you think that would be useful?

S31: I think if you were to say are any of these, do you think any of these are important in how you would determine causality or assign causality? Then I would have replied yes, I think they're all, you know, maybe some more so than others but assigning a 1 or 2 means well maybe it's not that important when probably it would be.

M: Okay, but let's say we design a tool and you know, you have to answer these questions with yes or no and at the end it produces a score [mmm hmm] and then based on that score you would know yeah, we'll assign it a possible or a probable [mmm hmm] or a definitely or what have you. Do you think that's a tool that you might use?

S31: Mmm hmm.

M: What sort of, what other features would it need to so that it would be useful to you? Is it too long, is it too time consuming, takes too much brainpower, is it something that you do anyway and it's not useful?

S31: Um, I don't think it's time consuming, I think any tool that you have that helps you to establish causality or not would be useful. **(time seems to be a large barrier)** So I don't, I wouldn't consider the time factor, I don't think, you know, something like this is definitely not time consuming. It would probably be best to spend an extra few minutes doing this to help you if you found it would than to not do it at all. Because then, like I said, later on you are trying to retrospectively figure out was it or was it not. So if we could determine it sooner with a tool then I think it would be worth the time. So time wouldn't be an issue for me. Um, I don't think it uses brainpower, if it's a tool that's assisting you then it wouldn't be using brainpower, in fact it's helping you relieve that stress. [laughter] And what was the other issue you were saying?

M: Oh, I was just wanting to know how we could make this useful and practical for you in your work, in your everyday working environment. Is it best on paper or on a computer or?

S31: Um, I like paper because you can pick it up and refer to it without having to log in and find the site and you know, bring it up on your screen and, and then you know. [yeah] So I like a tool on paper, it's tangible, it's quick [yeah] probably less time consuming than trying to search for it. [yeah]

M: Okay, good, thanks for doing that. [okay] Let me just see, I think that's, I think those are all the questions actually that I have for you. [okay] Do you have any final comments or questions you'd like to ask me? [no] Okay, great. Well thank you very much, I really appreciate this time, I know how busy you guys are.

Subject 32

M: As I mentioned we're interested in how causality is assigned to adverse events [mmm hmm] serious adverse events in early phase clinical trials. [right] Even the most experienced find assigning causality challenging. [mmm hmm] And many groups such as industry sponsors, clinical trial cooperative groups and research ethics boards they all expect prompt and sensible causality assessments. [mmm hmm] But as you know, it's not always that straightforward and if done poorly there are some implications. [mmm hmm] So we're interested in developing a tool to help efficiently and reliably assign causality [okay] and as I mentioned earlier, we feel that by better understanding your needs we can help make this tool more relevant to you. [okay] So do you have any questions before we start? [no] Okay. So first of all, I'd just like to ask you if you can recall recently a serious adverse event that happened with one of your patients that was pretty straightforward in terms of assigning causality [okay] can you think of an example?

S32: I just had two, febrile neutropenia which is pretty common in our

M: So what patient, the patient was on a trial?

S32: She was on a clinical, both of them were on a clinical trial yeah, with docetaxel and then the clinical trial study drug.

M: Okay so it was a combination of docetaxel plus [Avastin] okay yeah. And um, that patient experienced febrile neutropenia

S32: Both were admitted to hospital with febrile neutropenia. [okay]

M: And how did you assign causality in that case?

S32: Well for me it's the principal investigator that assigns the causality. But we just know that one of the toxicities of docetaxel is um, low counts and fatigue and

you know, just by knowing the toxicities of the specific chemo we could relate it probably to the docetaxel, but not 100%. [okay] Because the Avastin may be a factor in that, so it was primarily docetaxel and then a question of whether or not it might be the Avastin as well. [okay]

M: But for the most part that was pretty straightforward?

S32: Yeah, for me because I've dealt with docetaxel quite a bit so I know a lot of the toxicities and we see that frequently. **(experience is key)** Not always to the point that they're hospitalized, their counts, their neuts fall sometimes to zero, so obviously they're open to infection and that's usually what lands them with a fever and then in the hospital. But um, yeah, docetaxel is one that I know is going to cause that in most patients to some degree. [yeah] So that's how I know that, to assign that causality to it. [okay] When you're using a drug like Avastin or something that's new they do have their list of toxicities that come with that specific drug so you can kind of correlate it and look at it and say well it's not really a toxicity that they specify. It might be a minute percentage that get it but um, so we don't, we don't say 100% that it's the docetaxel, we have to sort of look at possibly the Avastin or the combination of the two. I don't know if that helps at all. [yeah]

M: Okay, can you give me an example of a serious adverse event that has occurred and it maybe wasn't as easy to attribute causality.

S32: Oh God, let me think, yeah we had one last year, what was she admitted for? God I can't remember now. I'm trying to remember what she was specifically admitted for, I think it was more depression. And um, what did they classified it as? depression and, I don't know what the terminology was but she was hospitalized for a few days, she just couldn't cope anymore. And I think it was, she obviously, a lot of it was due to the stress, having cancer and being fairly young and having kids at home. So we couldn't really attribute it to a study

medication. Um, I spoke to the doctor, the PI that was working with me on that trial and I said would you specifically think that that was a reaction from a study drug? and he said no. So I mean, I kind of rely on the investigator to know where the symptoms are coming from and if they could be attributed to a certain medication they're on. So I really rely on their expertise to know whether or not it's something I can relate to the study drug. I wish I could remember specifically what it was that they admitted her with. [that's okay, close enough] Fatigue or something like that, depression, she wasn't in very long. [okay]

M: So in that case it was a bit challenging because you weren't sure if it was due to um, just the normal stress of having a [cancer yeah] cancer diagnosis.

S32: Sometimes it's not black and white because it could be a number of factors. **(grey area again)** And when you factor in the fact that they're on chemotherapy and they're on study medication, and they're on pre-medication for you know, nausea, vomiting, whatever, they're on growth factors, they're on Tylenol for pain. So sometimes it's hard to attribute it to exactly one specific thing. You kind of have to say it could be a combination of their con-meds and their study medication and the chemo, so it's harder to give a causality. So usually a lot of times we just, we have to answer unknown because we're not, we can't specify exactly, possibly, could be related you know. And our CTO assessment sheets that we use um, we always like to relate the toxicity to the specific study drug that we're using. So I think we have a few options, one being likely, um, possible and then unrelated and unknown. So you kind of have a few things you can pick from. [mmm hmm] That helps us to be able to sort of look at it and say okay, she didn't have this at the last cycle, but she has it at this cycle, and is she still on it and how long? And then you can sort of get a pattern, if you have quite a few people on that same study you can see that maybe by cycle III they're all starting to have more fatigue. Or they're starting to have you know, changes in their fingernails, so you can see a pattern emerging.

M: Right as you have more patients enrolled you see a pattern happening.

S32: Yeah, well yeah, with the sheets that we have we can sort of look back and quickly say oh yeah, all of these patients seem to be doing this around the same time. So that sometimes helps assign causality. **(uses the term quickly suggests there is not a lot of time available to make these decisions)**

M: So this is sort of a baseline assessment, or it's a an assessment page that you use for.

S32: Yeah, we do a baseline assessment page and then we do, they're called clinical trial observation, so they're just sheets that we use that have all the toxicities. So each time we see a patient we review all of their toxicities since the last time they came in. [mmm hmm]

M: Are there any other tools that you use when assigning causality?

S32: Um, well of course you're using your protocol, so each protocol is going to give you a list of um, possible side effects for each drug that they're on. So that's a tool that we always use, you kind of refer back to the protocol, like is this a side effect that we're going to see with Avastin? Yeah, the protocol is huge, it really gives us, it's sort of our bible to work from when we start because that will give us an idea of what we're, what to expect. You know they may say that a certain percentage of patients on drug x are going to experience bleeding or gum soreness or. So we know right away if we see a patient we can say yeah that's, we're pretty sure that's related to the study medication because that's a side effect that they've noted in the protocol. [okay]

M: Are you aware of any other decision-making tools in helping you assign causality?

S32: Not that I know of. [okay] **(not aware of the tools that exist)**

M: What would you say are some of the challenges with assigning causality?

S32: Well I think I mentioned it before, you're going to get some toxicities that kind of overflow into you know, it could be a couple of different categories. It could be your study medication as well as your, your chemotherapy. So you're getting, I don't know, something like, I don't know, say neuropathy of the hands and feet, well they're, there's different drugs that will cause that. We know docetaxel will cause that, but then you'll get a study drug that may have that same adverse effect. So trying to directly relate causality to that sometimes is difficult when you know that it could be experienced in two, two different, or three different medications. [yeah, okay] **(so many confounded variables really impedes decision making confidence)**

M: Any other challenges that you've encountered?

S32: In causality [yeah, assigning causality] well I mean, I think, I find it difficult because I don't, I mean I have a bit of a medical background but I'm not a doctor so I don't know. When somebody comes in with something that's not common, you know, how do you rate that. If it's not on the list in the protocol and it's something you haven't experienced, sometimes that's difficult [mmm hmm] to make that judgment. Is this just a specific case with that patient or is it possible that it's a reaction or a side effect or toxicity of the medication? So that's sometimes is hard, something that you don't see frequently, how to grade that or you know, the causality of that sometimes is difficult for, for somebody who is not a doctor to pick that up and say this is definitely, and we don't really have a tool for that because there's nothing that you can really refer to. You have your protocol and you know, you have your list of side effects from the chemo drug so you kind of go by that and if you don't see it in there, it's hard to grade it, like where do you put that? you're not quite sure you know. [yeah] So unless it's in

your protocol it's hard to find out where that comes from. [yeah, okay] **(protocol is a commonly used and heavily waited resource when assigning causality)**

M: What do you do in that case?

S32: Go to the PI, you go to the principal investigator and say, you know, do you relate this to the study medication? And they're good to tell us whether or not it's related.

M: Do you have any concerns about how causality is being assigned?

S32: I wouldn't say I have any concerns about it really, I mean, it's pretty straightforward, I mean if you don't know where the causality is coming from you, you go to your PI. Because ultimately they're the responsible person and they're the ones that should be able to tell you that it's either related or not related or where, what the causality is so. [mmm hmm] I count on them.

M: Do you have any concerns about their causality assessments?

S32: Sometimes. We have to, I mean you have to be able to trust them, hopefully, they're taking on the study, they're responsible for it. I mean you can go to the sponsor and actually I do that a lot too, you know. Just call up the sponsor company and say, you know, I'm kind of stuck here, I'm not sure if this is, you know, could this be a toxicity of your study drug, do you think there's a possibility. And we've done that too where you know, you'll just email them or call them. [okay] And they have a pretty, I mean they have a very broad knowledge of the drug that they're putting out there and what they've seen. And of course they're getting data from everywhere so they should be able to tell us you know, if that's something they've seen before. [okay, good]

M: What external influences or pressures from third parties have you felt when assigning causality?

S32: Hmm, not too much. Sometimes you'll have a patient on a study where the oncologist would like them off and for whatever specific reason or on, you know, they maybe say that ah, it's not a cause of the study medication. Where you're kind of thinking oh I don't know, I've seen this a few times and it seems pretty clear to me. But they're sort of saying 'no it's not a cause'. So I mean to say there's never been an issue around that.

M: And that's from the physician?

S32: Yeah, because they want to, sometimes they will part the sea to keep their patients on the study. [really?] Sometimes. [why do you think that is?] I don't know, because obviously when they're affiliated with a study and if the study is doing well, they want to you know, have their name affiliated with that study and the more patients they have on the better it looks for them and our site too so. **(feels some physicians are biased, may be more focused on the appraisal of marketing a drug, then true concern for the patient-however there are severe consequences)** But I think they're all pretty good at, I mean we have to report all SAEs there's no way around that, you have to do that, we report it to our ethics and our report goes out to the sponsor so. If it's something that's causing the patient to be hospitalized or it's harming the patient there's no way around it. But I don't think, I have never personally had any major issues over that. [okay]

M: So from your perspective then what would make assigning causality easier?

S32: I guess, I don't know, that's a good question, what would make it easier. I mean obviously a book that said all the possibilities of side effects and, and then how to relate them. Like yes this is related to drug x or this is related to chemo

whatever. It would be nice to have a tool that told you directly whether there was a possibility of causality. Maybe the Internet tells us that I don't know, I don't have time to run back up every time. But yeah, it would be nice to have some kind of manual that said you know, this side effect is the causality of from whatever. It's not possible though.

M: That might be asking a little much. What I'd like to do now is I'd just like to ask you to do a little exercise for me. This was an algorithm that was designed by a researcher [mmm] to help in assigning causality. Our thought is that if we can modify this a little bit to suit our needs for the early Phase oncology clinical trials study that that might help make things a little easier in terms of thinking it through. So I'm just wondering if you wouldn't mind reading over those 10 questions and crossing out any that you do not feel are not relevant to the oncology, early Phase oncology clinical trial setting.

S32: I don't quite understand this one, was the drug detected in the blood or other fluids in concentrations known to be toxic? [mmm hmm, what's confusing about that one?] You're talking about the study drug I'm assuming. [yes, yes] So was the study drug detected in the blood in concentrations known to be toxic? [is that something you would normally have or?] No because I mean you wouldn't administer a level of drug that would be toxic for one, I would hope. [yeah, well I guess] If it was known to be toxic, I don't, that question is just confusing for me so maybe it's just me. [cross it out then, go for it]

M: Okay [you want these ranked] Yeah, so now if you could just rank the remaining ones in order of importance, so which ones do you think are most important. So most important would be 10 and you could just kind of work your way down from there I guess.

M: Okay, great, thanks. Most important was did the adverse event appear after the suspected drug was administered, that makes sense [mmm hmm] that's

pretty important yeah. Did the reaction improve when the drug was discontinued, good yeah. Um, there are no right or wrong answers here, it's just interesting to see what people have done and we're going to try and summarize it all. Least important, was the reaction more severe when the dose was increased, or less severe when the dose was decreased, why did you rank that so low?

S32: Well to me if you answer these questions that automatically is answered. [okay] And the severity is very hard to rate in some cases because if you we're some things are, like if you're grading something that has a value to it, you can easily assign severity to it. But when it's subjective, like how a patient is feeling or how sore their mouth is or you know, how much pain they might be experiencing, it's all very subjective to each patient. So severe to one person might be you know, moderate to another. So those kinds of things I find, unless you can assign a number value to it I find that hard to grade. Because some things are very subjective, pain, those things are, in my, I find personally hard to grade. [okay]

M: That's actually a really good point yeah, okay. So what did you think about this, so if we were to, never mind the fact they are ranked now. But if we were to give this to you as a tool to think about when you're assigning causality do you think that would be useful.

S32: It would be useful, I would like it smaller, I don't want to have too big a form to have to peruse to go through it to figure out. It should have you know, a few very pertinent points that should get you right to the causality of it. One of them being, did it start after the drug was administered? When you stopped the drug did the reaction go away? Like very specific questions that don't get too wordy and don't try to get into too much of the detail right away that can give you an idea of how you're going to assign the causality. **(simplicity is key)** I wouldn't want that many points on it I think [yeah] I think I would want less [fewer] yeah. A lot of those are sort of repetitive, but just in a different way.

M: Yeah, they overlap a bit yeah, a lot of people have said that. Okay, great.

M: And then lastly I would just like to ask you a little bit about the training that you've received. [mmm hmm] So um, can you tell me about how you learned how to assign causality to adverse events, what kind of training did you have?

S32: There's no formal training really, you just kind of got thrown into the position. I mean, the training is really on the job training. It's the more patients you see, the more that you start to understand that there's going to be certain side effects and toxicities that you're going to see in cancer patients. And then you start seeing them specific to a specific drug and you just, it's really learn as you go. [and what about yeah, yeah] Training, specific training comes with each new study that we open. So when you open up a new clinical trial you attend investigator meetings where they explain everything you know. How, what drug, this is the drug we're using, this is how the drug works, this is how the drug is you know, produced, this is how it's going to work in the body, this is what we're hoping it's going to you know, achieve. So you learn all that from the sponsor that is opening the study. So a lot of what you're going to be taking back is stuff that you learn from them.

M: And do you usually learn how to assign causality at those investigator meetings?

S32: Yeah, they do, they talk about how you're going to report adverse events and what to look for. They usually have a book, we usually have a book that lists adverse events. Possible side effects and then it'll have you know, the very, the common ones, the not so common, the almost never seen, highly unlikely, so they're sort of

M: Is that something separate from the IB or?

S32: It's in the, each specific protocol. The investigator brochure has that too but the protocol will have it in it. And it's usually, when we give patient's consent it will also be in there. We'll have categories that will say these are the side effects that you might experience or are likely to experience. And then it sort of goes down the list and it breaks it to likely, less likely, highly unlikely you know [mmm hmm] so they know what to look for. So that's a good tool for us if we want to quickly, you know if you get called down and it's not your study and you know, well the doctor is saying well this patient and it's not a study you've done. You can quickly look at the, the protocol and say, oh yeah, it's, it's you know it's in there but, so that will give you a quick idea. [right] If you don't know the study very well or if you're not sure which drug they're using.

M: So those investigator meetings are pretty, pretty important.

S32: For us they are, I mean, that's what

M: Do you get to go to them or is it usually the PI?

S32: No we do, the study coordinator goes and the PI, because we're coordinating the whole study and we're the ones that usually are telling the PIs the stuff you need to look for, they come to us. So I think it's really important that CRAs go to that because we're the ones coordinating the study, we know that study inside and out. We know what patients are eligible, what makes them not eligible. You know, there are points where we need to go to the PI and say you know, we need to stop this patient because we're seeing this or. So yeah, it's really important, it's huge. [yeah]

M: What additional education about assigning causality do you feel needs to be made available?

S32: Um, be nice if the site would give you that kind of training, but it would be really hard to do I think because we all have different studies that are all, mind you, each area seems to see the same. **(feels education on assigning causality would create greater consistency between professionals)** I mean if you're working in lung, or if you're working with GI or whatever, you tend to see the same drugs over and over again. [yeah] So you know a lot of the causality just from you know, repetition. But if you kind of, you know, as a, as a breast study coordinator for the breast site, I don't see a lot of the drugs they use say in GI. [yeah] So when I get a GI drug I really, I don't know how to assign causality to something. So, it would be helpful if the site did on site training [what do you mean the site, your] our site here. Like our clinical trials office if they had, I don't know, one or two days a year, like a workshop that helped with that. I don't even know if it would be possible. [I think anything is possible] Yeah well.

M: So like a one-day workshop you think would work well?

S32: Yeah something like that.

M: What would be included in the workshop if you could have, if you could design it yourself what would you do?

S32: Well I mean, obviously it would be nice to have um, you know the scientists or the doctors that work with these and have, you know, the ones that come up with these study drugs and know what causalities may come up. Or what toxicities may come up and what causes them. And it would be nice for us to learn what actually causes them, like what's actually happening when a patient is having this type of side effect. Like what's going on with the body and how it's reacting with the specific drug that could be causing that causality. [yeah, okay] I don't know [yeah that's good] **(a more biological approach to understand toxicities could aid in causality assessment)**

M: I think that's all the questions that I have then, do you have any final thoughts or comments or questions?

S32: No, sorry it's after 2:00.

M: I know, it's getting on in the afternoon and people are tired. Well thank you very much.

Appendix 10: Themes

Theme 1: Coping with Uncertainty

Definition: These professionals use a variety of methods to cope with the uncertainty of causality attribution.

Subthemes:

- Consider protocol drug
- Consider other drugs
- Cognitive Approach of considering all variables
- Take comfort in recognizing grey area
- Temporal association
- Erring on the side of caution
- Rely on their experience

Quotations:

- Certainty is very difficult to achieve- S01
- I think that the probable, possible, etc scale is better, it just gives more room for interpretation of the interpretation.- S01
- Yeah and yes and no is desperately frustrating sometimes because things are grey like, you know, if it's unlikely but it's still possible then saying you know, is that yes or no because that's hard.- S01
- There is a lot of background noise in side effects, what side effects may be caused by other drugs, disease.- S01
- But we're still stuck with you know, these vague situations with the problems we've discussed and I don't, it's not clear.- S01
- Most of it is kind of intuitive you know, so I'm not sure.- S01
- Um, sometimes it's grey, you know, maybe could be and that's the difficulty.- S03
- And I think a lot, a lot of that has to do with you know, how do you make the decision, it's difficult sometimes, sometimes it's pretty straight forward that they're experiencing an adverse event that is know to occur with the study medication.- S04
- I think yes or no becomes very hard and we're not always sure you know. And there's always that element of doubt about it. But I think you have to be able to say how strong or weak your doubt is and when you have the graded scale it just gives you some flexibility to do that.- S05
- That is a challenge in that typically when patients go in to clinical Phase 1 trials they have advanced, often refractory cancers and ah, needless to say, significant ah, medical problems at the beginning and throughout the clinical trial.- S06

- I think it's better to maintain a sort of a graded scale because I don't think one can be that definitive. With the number of resources you have, it's only a matter of being able to document and have there as a possibility.- S06
- Problems, first of all you're never definite, definite, hindsight's always 20/20, so looking back a few months later you can sometimes get a more clearer picture of what, like analyze the situation a little bit more. Sometimes when you're right in the situation and you have to, you have that responsibility of assigning it right then and there, you don't have all the information right? You don't know how it's going to end, you don't know, um, if, if, why it happened or anything. You can analyze the situation after it occurred and everything has evolved then it's sometimes easier to go back and go well this and this happened we can do that. So assigning causality sometimes at the time is sometimes clear cut and sometimes very difficult.- S07
- Oh, who knows, whenever you get an algorithm it's always like the yes/no's sorts of things and sometimes there's a grey in-between. So sometimes you have to kind of think differently.- S07
- You always look at, I mean there are always so many other confounding variables in this population, especially if their disease is starting to get a bit worse. They go on other medication, right which can impact, you don't know what these newer agents do with any of the other medications that are out there. There are just so many variables that can [yeah] affect, drug-drug interaction you know and drug-disease interaction, drug-foods. I always make a point of asking patients are they on any over the counter or complimentary therapies because they may not think, well I'm not taking any medication but they're on all these herbal or [yeah] just lots [lots of unknowns right?].- S09
- I like the scale because yes/no is pretty black and white and often there are many scenarios where you're just not sure.- S10
- Often these patients are just, have such complicated histories, you know, they're prone to other medical problems.- S10
- The challenges are particularly in Phase I trials these are, these, they all have their advanced disease, they often all have been through numerous other treatments, some of them have been heavily pretreated. Many of them are not of the greatest performance status and so they have a lot of other co morbidities or symptoms that can merge and play a role. Sometimes these brand new drugs we really don't know. We don't have a lot of information, that's why we do the Phase Is. And how much weight we put on what is seen or not seen in dogs or monkeys or whichever animal work they have done it on, large animal work done, kind of you know, there's not a lot of data there, so in the end if you don't have a lot of data to work with and you have patients, it does become very hard.- S13
- Yeah, [yeah] yeah I think so. [okay why?] Well because there's a, it may help you sometimes in the dilemma where you in this grey zone of serious adverse event where you think about what to, what to assign to this SAE.

If you have a clearly unrelated or clearly related SAE that's easy but the, the vast majority of SAE's is probably somewhere in between..- S14

- That's where I think issues of attribution become very difficult.- S19
- But you have to, I think you have to assume that you don't know enough about the drug that it could be drug related.- S20
- I think a lot of it sometimes is the background noise from patient or the disease. And how do you know the symptoms are not related to the cancer or to underlying symptoms from other comorbidities from other chronic diseases the patient may have? - S20
- Well sometimes it's difficult, somebody, say somebody with chest pain who has plural metastasis it's really hard sometimes to know whether this is related to pulmonary embolism. Then basically have to do the appropriate diagnostic imaging which in that case would probably be a spiral CT scan to try and sort some of that out. Um, what other symptoms? say patient fatigue, ah, well that can be really difficult for instance, it could be related to disease, study drug, could be related to psychologic factors, some change in the patient's environment, who knows? And that could be, and you have to look at all those and figure out which is most likely and then it's you know, and have there been changes in those areas that might explain it? Um, and if there's more than a couple of possibilities you have to kind of use your judgment which is more likely.- S20
- Just that there's more than one possible explanation for a lot of toxicities that you see. So as you say, PE can be due to the drug or it could be due to the cancer and maybe they would have had that PE even if they weren't on the drug or because they're immobile or any number of factors. I guess it's just that there are multiple factors at play. I'd say that's the most difficult aspect of it. And plus the fact that they may be on other treatments, like they may be on something for their hypertension or their diabetes [yeah], they've got often multiple medical problems aside from the cancer.- S21
- And then it becomes difficult for me, but then you're forced to make some kind of a decision.- S22
- To the causality [oh the causality yeah] because you have to react in some way. So I had to think this morning for example this ocular side effect, was it due to you know, drug A or drug B or the combination. Or was it due to something incidental like you know conjunctivitis or something. So you have to think about alternative causes, alternative explanations. I mean people with cancer get many symptoms from the cancer that are not necessarily due to the drug, they may just be due to the underlying disease. And of course a lot of people have comorbidities because they're elderly and have a 101,000 things wrong with them. And you know, is it just something incidental. So I think one of the important things in the causal reasoning is, is to be aware of what the possible causes could be. You know, it's due to the experimental drug, it's due to some other drug the patient may be taking or may have just started taking. It could be due to the underlying cancer, it could be due to some other illness that may

have occurred or that may have already existed like diabetes or angina or something you know. So I think critical in the sort of, the kind of cognitive approach is the realization that there's a whole slate of things which could possibly either alone or in combination have resulted in this phenomena.- S22

- But every now and then it's tough, like what happened this morning for example, it was difficult, it wasn't clearly obvious to me what was going on.- S22
- You might argue you know, causality is difficult, causality is not simple. [no] You know, there's different kinds of causality, there's the kind of relationship where something is sufficient on it's own. [right] There's another kind of relationship where something by itself is not sufficient on it's own but it's necessary. [and then there's] And there's relationships that are where you have it's neither sufficient nor necessary but it nonetheless contributes. So it's actually, on the one hand you're saying well just attribute causality but there's actually a more profound and fundamental understanding of causality with respect to well what type of causality? Um, which is important I think because it does help you manage the situation you know, so sometimes I don't think it's possible to be 100% sure.- S22
- You know, this is caused by drug X or it's not. And in a sense I don't like that because, I know, I just don't think it represents the reality and the reality is sometimes there is an element of uncertainty.- S22
- But, but even if you stumble on a strategy that's effective it doesn't necessarily mean that there aren't other strategies that are also effective. [sure, yeah] So this just speaks to the complexity of this, especially when you're dealing with two drugs.- S22
- M: So definitely dealing with two or more drugs in combination is a challenge [yeah] in terms of assigning causality, are there any other challenges? - S22
- So it's, you know, these things are in a way matters of life and death, they can be.- S22
- And I think a lot of things can happen under the, under the banner of uncertainty. You know, you can be forced to under, I think that uncertainty is at the heart of this, its at the heart of this. And I don't think it's a matter of honesty or dis, I think it's uncertainty and how do people cope with uncertainty? And I think that this actually is the measure of whether enterprises succeed or fail. You know, it's how they deal with uncertainty. So I think for example one of the differences between successful businessmen and unsuccessful people in business is that the unsuccessful people don't know how to deal with uncertainty. Um, because life is full of uncertainty and you know, it's possible to be panicked into, into making a wrong decision. On the other hand it's also possible to be paralyzed into not making any decision at all. [yeah] So when you see these kind of little human dramas played out in this situation as well because, but I think it's a mistake to not allow the physician to be uncertain when he or she is genuinely uncertain.- S22

- Well more so but there was a lot of problems with some of the toxicities as well, all the patients were having serious adverse events. But they were also very ill patients and it's very hard to separate that out at times.- S23
- Nothing in particular pops up, I mean I can see there are some areas that obviously are a little grey as to which way the assignment should go, whether it's definitely related or somewhat related. - S24
- Um, ah, well just that, that, it's always, you never know whether something, there could be that chance that you don't know whether something could be related if it's a new event if it's happening with our patients.- S25
- Well I guess just trying to determine which drug could be causing the adverse event, you know if it's, you know they could both be causing it, it could be one or the other so you need to do.- S27
- And pre-existing conditions in the patient if they have you know, other health problems that could be contributory to some symptoms. You know, and sometimes it can be as easy as just the person themselves, some people will say they're perfectly fine when they're not. And other patients will elaborate on you know, how they're feeling and might be exaggerating a little bit. So you know you have to try and understand the patient themselves as well.- S27
- So quite often I think it can be multi-factorial, it may not be just due to the one thing [yeah] so it's complex, pain is complex. So I don't think you can, sometimes it might be obvious, I mean if someone has bone mets and they come in and they have a fracture. That's pretty straightforward, it's their disease, but it may not always be that straightforward.- S29
- So it's really, it's, there's, it's a combination of factors when you're making decisions, when you're designating causality.- S30
- So sometimes there are grey areas and at the time it might be difficult but retrospectively by continuing to look at data after the fact then you're able to um, to decide at a later date.- S31
- It's tangible evidence that there is a toxicity. But something that is not a direct result but could subsequently happen is I think a grey area, and it could probably, it might have been, we don't know for sure. [yeah] So that's why I say it's kind of a grey [yeah] a grey area.- S31
- So sometimes it's hard to attribute it to exactly one specific thing. You kind of have to say it could be a combination of their con-meds and their study medication and the chemo, so it's harder to give a causality. So usually a lot of times we just, we have to answer unknown because we're not, we can't specify exactly, possibly, could be related you know.- S32
- A study drug that may have that same adverse effect. So trying to directly relate causality to that sometimes is difficult when you know that it could be experienced in two, two different, or three different medications.- S32

Theme 2: Subjective Judgments

Definition: There is rarely objective evidence when assigning causality, making it a very subjective process, full of inconsistency.

Subthemes:

- Variations in experience level
- Variations in work ethic
- Patient subjectivity
- Lack of standardized tool

Quotations:

- I don't know that I have, I think, I can certainly imagine however, in one's own trial whether there's going to be a bias and you don't want side effects to be attributable to your drug, um. [like if you were the PI] Right, if you were the PI easy to imagine and it may or may not be conscious though. And on the flip side is you may have a prejudice against the drug because it is prior reputation, or difficulty of administration or something which you know. I can't say that personally in short I've felt anything in particular, but it may be lack of experience to date.- S01
- And, and ah, um, what really annoys me is when investigators at other sites don't pay attention to this and let's say there's an SAE they attribute it to you know, very likely study drug.- S03
- My head.- S03
- Just my clinical judgment.- S03
- My common sense.- S03
- I mean it's almost from the experience we've had with drugs.- S03
- So I think, those ones are okay because you're basing it a bit on personal experience [yeah] and a little bit on what's published.- S04
- So it's more like each case, hopefully, you know, the fear is that you're not consistent I guess, that you know, you're scoring a patient differently, that's, that's the fear.- S04
- Basically all one can really do is, based on experience of managing these people sort of know what to expect as their cancers progress and as their regional stages of life, as in previous experience in managing.- S06
- It's really based on experience at this, at this stage. So really it would depend on a, an experienced investigator who has managed a lot of the specific patient population to in my opinion, accurately determine if this is something that's related.- S06
- That's a clinical judgment based on what's happened to the patient.- S06
- So it is experience.- S06
- Yeah, I mean you use your clinical assessment and um, and it's really process of elimination and if nothing else comes out.- S09

- Well I think just the fact that there, there isn't a systematic way to do it, that it often is based on hunches and feelings as opposed to a rigorous method or measurement tool.- S10
- So I think it definitely depends, again, very individual, depends on the patient, depends on your personality, what you're asking. If you're asking the appropriate questions or not, I think that that makes a big, a big difference too.- S11
- Oh gosh, it's hard to say, again, every patient is different. Some patients, um, some patients I think it's easier to leave everything open and let, just leave it as a blank slate, let them tell you everything that's been happening. Um, some patients if you do that won't tell you anything. So some patients, not prompting but some patients you need to I think go through a list of questions and ask them about specific side effects, problems, even possibly body systems and leave it open that way for them to suggest things to you. Um, again, um, I find it's, again reporting is very different from person to person in terms of the clinicians.- S11
- Um, and again I think that's very subjective for the clinician also the way the patient describes things. I could consider it a grade 2 whereas the physician could consider it grade 3. - S11
- I have to admit that is very subjective at times.- S13
- Um, well to be honest, not really I think you just go on what your best clinical judgment is or what your patient's status is.- S13
- But ah, um, you know, I think it's a very subjective process, that's the problem. And subjective in terms of ranking them or associating but also subjective in how much effort people actually put into the work. And I won't say I do it all the time but you know, I think in terms of how much background work one does in trying to understand the causality with each one trying, if you're not certain, if you are certain it's very easy. Perhaps, if you're not certain are you going to spend that extra time to pull out the IB or talk to you're you know, pull out the protocol and actually do the best.- S13
- So unrelated, definite, possible. Like what's the unlikely and probable versus possible versus probable, you know, where do you draw the line? Again, it's very subjective.- S13
- But ah, um, you know, I think it's a very subjective process, that's the problem. And subjective in terms of ranking them or associating but also subjective in how much effort people actually put into the work. And I won't say I do it all the time but you know, I think in terms of how much background work one does in trying to understand the causality with each one trying, if you're not certain, if you are certain it's very easy. Perhaps, if you're not certain are you going to spend that extra time how much background work one doesto pull out the IB or talk to you're you know, pull out the protocol and actually do the best [7:30].- S13
- But that is basically based on, on the situation and your experience and not on any formal rules or algorithms or whatever.- S14

- Well it's so subjective, in the end, for the majority of SAEs which are in this grey zone of possibly or likely or unlikely related, it's a very subjective, a very subjective thing.- S14
- You know, where the same event can be attributed differently because a lot of things, it's a subjective assessment. It's not as objective as it should be, I think that's what makes it a challenge.- S18
- No. I think we basically use our medical judgment and the sources of information.- S20
- No, it's kind of, for me it's like an intuitive process, and I should also say that sometimes the CRA's do it.- S21
- Um, I think it's a long way from engineering right now and I think a lot of it is gut feeling and kind of intuition.- S22
- Well I guess one of the things that I've always had a difficult um, thing to grapple with is that there are too many, often there are too many categories of relatedness. [okay] You know, like definite, probable, possible, unlikely or not, do you see what I mean? [yeah] And I think that those are fairly subjective definitions that will vary from person-person. You know, what I think is unlikely is not necessarily what you might think to be unlikely [mmm hmm] and so um, again the assigning of causality there could be sort of chance depending on the interpretation of the definition by the individual physician.- S26
- Well as I said I think sometimes it's arbitrary and it depends upon the physician's interpretations of the definitions of you know, these different things. I think it depends a little bit on the physician's past experiences, expectations and biases with respect to the class of agents and so on.- S26
- Well we probably don't pay as much attention to it as we should. I mean a lot of the initial information is prepared by the CRAs or the study nurses and I think in a practical everyday busy clinical environment we have these things coming across our desks to be signed almost on a daily basis. And I'm not sure if we think about it as much as we should, if we give it as much attention as we should, because it's just another thing to be signed. [mmm hmm, yeah] And there's been sort of very little attention paid to it in sort of the clinical research area.- S29
- Like pain, pain is subjective, fatigue is subjective, I mean you can try and quantify it but if you think that the study, that the causality, that fatigue is due to the study drug you're not going to have objective evidence. [true] Weight loss, well I guess if you have weight loss you can measure them in pounds but it's not always going to be there.- S29
- It would have been nice if we could have established causality unanimously but. [yeah] So I say going to the physician but if there is more than one involved there can be more than one opinion.- S31
- But when it's subjective, like how a patient is feeling or how sore their mouth is or you know, how much pain they might be experiencing, it's all very subjective to each patient. So severe to one person might be you know, moderate to another. So those kinds of things I find, unless you can

assign a number value to it I find that hard to grade. Because some things are very subjective, pain, those things are, in my, I find personally hard to grade.- S32

Theme 3: Insufficient Resources

Definition: There are a lack of resources available, or made known, to assist these professionals in assigning causality.

Subthemes:

- No causality tool
- Lack of detail
- Communication issues
 - Sponsor and interviewees
 - Patient and interviewees

Quotations:

- So there's often not a lot of guidance it's more winging it.- S01
- Yeah, and I would say timing is the most important factor. I mean, other factors, we don't usually have dose as a, as a ah, we don't usually have doses in the same, different doses in the same patient to be able to judge a dosing relationship- S01
- As previously mentioned dose, you know, often we don't have a dose relationship that we can look at.- S01
- Supposedly one of the criteria for causality is something like a dose response relationship whereby more of something causes more of an effect. And a patient typically, although we may have that in a cumulative dose, we don't have different doses from cycle to cycle necessarily. So you can't say when you had a little bit of this you felt a little nauseated, now that we're giving you 10 times more you're feeling really nauseated. So we wouldn't have that information typically. - S01
- Actually not any that I know of.- S04
- I can't say that there any actual guidelines that I know of or that I specifically follow.- S04
- Oh, very little, I mean I think um, a lot of the pharmaceutical sponsors that we did some studies with, had some training modules but not necessarily for causality mostly for adverse event reporting- S04
- I normally don't use anything particularly that formal.- S05

- There hasn't been any formal training, yeah, there's hasn't been anything formal.- S05
- No I'm not aware of any.- S06
- Um, I would say that more resources would be good for investigators, more resources at their disposal. [what sort of resources] Well, resources through the sponsor [for what] for information [oh okay] more information as to whether, you know, if you have questions about a certain event. And for example you wanted to understand the drug's pharmacology better and try and determine you know, in some way could there be access to that information beyond the IB. The opportunity to discuss on a regular basis with other investigators, how the trial is going, um, through conference calls is a good idea.- S06
- Lack of appropriate information.- S06
- Well I think if there's a, I think there is a certain distance often between the clinical trials nurse and the physician.- S06
- No not really, using just yeah, anything.- S07
- Well usually there's teleconferences and other meetings to discuss what's happening with other patients. But a lot of times communication isn't as good as it could be.- S07
- We should be involved in as much of those discussions just so everybody is informed. I haven't done a lot of, so I don't know what they do to keep it up but sometimes you do feel a little bit, you have no idea what the other people are doing. And it would be a little insightful as to how they're doing it, yeah.- S07
- Nothing formal. Sometimes in start up meetings or something like that they'll, they'll say a little blurb about assigning causality but they won't really give like formal education as to what, we should use this tool or anything like that. It's mostly a set reaction sort of.- S07
- Imprecise science! I am not, I mean I guess to have definition, I mean more clearly defined sorts of definitions of the terminology would be most, would be the thing that would be most helpful. [which terminology?] You know, in terms of the causality terminology, so more clearly define what people mean by unlikely, possibly, probably, you know definitely related. And at least people are using the terminology you know, in a similar fashion. - S08
- No, no I'm not aware of any.- S09
- I think it would be beneficial for all of us maybe to spend a bit a time with them and see. Or even with the data management, I don't know what they do with the data management part of it. [yeah] And I think it would help us understand part of what we're doing too when you see how companies or CRO's try to collate the information we send to them. And then what it can do in terms of, you know analyzing the study or.- S09
- I'll be honest and say I don't really have any [really]. I don't have any tools that I use.- S10
- M: And then um, do you know of any tools that are available to help in assigning causality? Have you every used any sort of a decision tree or an

algorithm or [no] something like that? No. [no] Do you think that would be useful?

S11: I do think that would be useful um.- S11

- A lot of the times I find it's hard and I don't think it's an on purpose thing from patients, but I don't necessarily think that we do get every single bit of information all the time.- S11 [yeah] I think different things are reported to different people, depending on your position, whether that be chemo nurse, clinical trials nurse or the physician.- S11
- I've had no formal training [no] actually.- S11
- None. [no] No, well I mean, I guess I shouldn't say that, none in terms of standardized criteria that's for sure. Resources, unless you mean basically going back to see maybe the investigator brochure and trying to understand some of the toxicities.- S13
- No, not that I'm aware of, not that we use here that I'm aware of.
- Um, more information from the sponsor I guess in terms of um, side effects of the drug.- S15
- Are there tools out there? [laughter] no I don't. [okay].- S18
- I think it's human nature to forget things [okay, forget] and obviously if it's a very serious event, it's going to be recorded and you're likely going to hear about it in some way. But not all patients understand that in a clinical trial that we're also interested in the side effects of the treatment. And in a Phase I actually toxicity is your primary endpoint. [mmm hmm] But the patients of course feel that they're on the treatment to help their cancer [yeah] so there's a little bit of a disconnect there. So they're more interested in what the drug is doing for their cancer and they kind of are hunkered down with the idea, many of them are very stoical right [yeah] they say I'm going to put up with whatever side effects I have to put up with um, to get through this treatment because it's going to help my cancer. And I think that's, that translates sometimes to a lack of reporting of events. I think that some patients may also perceive that you know, the doctors or nurses don't want to hear them complaining right, they just feel that they'll sound like whiners right.- S19
- Besides the patient, family members, maybe differences in behaviour, maybe some psychologic or neurologic issues associated with the medication because we just don't know enough about them, ah lab work, imaging results sometimes [okay] and the physical examination.- S20
- Nothing formal.- S20
- Minimal at best [okay] basically on-the-job training. I think all the CRAs we basically self-train or train each other as we go.- S23
- Yeah, um, yeah, obviously we haven't received any training for it but um, I'm not sure that we're the ones who are actually expected to come up with that determination. - S24
- So the physician meets with the patient [mmm hmm] and afterwards they come out and they dictate what sort of went on. [mmm hmm] And often times it's not extremely detailed, is that what you're saying? - S24

- Yeah, more detailed information I guess, other than what's in the consent form, having a list of expected events and maybe, some of them put in the percentages of what the patients have already experienced. So yeah, I guess that, just a more detailed sort of, um, like I was saying we go to the dose modification and it will list sort of what the expected toxicities are and the rules to follow. So maybe to have some kind of I don't know, chart or information in that area to go to, to see what we're looking for and how they expect us to assign the causality.- S25
- But other than that um, as far as education as to how to assess the causality [yeah] I would say that's really minimal to none.- S25
- Trial and error I guess. I mean the only, the only lecture I've ever heard about is, I've heard A speak once, but other than that you know, really nothing. I mean you'd ask other more senior investigators what they would say for this particular event and so on. But otherwise, there was no formal training.- S26
- Well, most of my studies are also sponsor studies and they tend to make the wording vague on purpose. [laughter] Probable, possible [the wording of what] probable, possible, definitely related, possibly related all the, so sometimes that can be a challenge if it's something you haven't encountered before.- S28
- No. [no eh, you don't use any?] No, in fact I think people tend to lean towards putting it, like when they're not sure, and most people are never 100% sure, they'll say you know either probable or could be. And I think we see a lot of "could bes" more than any other.- S29
- There's no formal training really, you just kind of got thrown into the position.- S32

Theme 4: Apprehensive Causality Attributions

Definition: There is a general fear of making an incorrect causality attribution that may result in rather severe consequences.

Subthemes:

- Fear of under attributing causality to the drug being tested
- Fear of over attributing causality to the drug being tested

Quotations:

- I think it can interfere, the inaccuracy of it can interfere with drug development and can potentially in the most extreme case, kill a drug. Or I suppose on the other side allow a drug to go ahead when side effects are overlooked. Although if, if you have a bunch of us who are calling unlikely things possible, because you know, we're not really sure because it's just subjective. And the FDA looks at that or the investigators look at that and decide, you know we just have too many pulmonary embolisms and they're all possible, as opposed to unlikely, you know, it can impact what

they do with that drug. They may change the dose and lose effect or they may stop the trial or whatever. So there's risk to the drug and to the patient.- S01

- If it's done incorrectly, it's a pain in the ass for all the trial nurses and all the invest, all the trial doctors all over the world because it takes time to sort out.- S03
- There's, there's two concerns, I think one concern is you know, over assigning causality. Because patients are, they can get sick, morbidities, multiple medications, actually a lot of reasons and it sometimes it's easier to blame it on the drug. But I think my fear is that if you, if you do that liberally you'd be, not discrediting the drug but you're not um, it could lead to dose reductions, could eventually work their way into an ineffective treatment schedule for that. If you saw a whole bunch of side effects that you thought were you know not really related to the drug and that led to that drug being less developed in a certain disease. Maybe you're doing a dis-service to that patient population, so that's one, that's one concern I have. Perhaps over-assigning causality just because of the complications of some of the patients on the program is my biggest concern. And the other concern is, the other, completely opposite really is the not assigning causality and then drugs are allowed to develop. And then it's only when you start getting into Phase 2, Phase 3 studies that you really, adverse events really show themselves. And you're thinking well why wasn't this picked up in the Phase 1 or 2 studies? [yeah] So I think you can go either way, you can make errors on either way, one way you might kill a drug that might be successful and on the other way you might let a drug develop not carefully enough.- S04
- I mean the biggest stress, not that I've had any stress about it, but the biggest issue is assigning causality that could result in a Phase 2 program going to a lower dose or something like that or you know a ineffective dose for a given cohort of patients is a concern, whether you're doing the, you made the call because that's often a critical step in a clinical trial.- S04
- There you're getting, you're, you know it's hard to, to, how, how strongly are you going to implicate the study on the side of implicating the study drug just from these issues.- S05
- Yeah, they are really, I think in some cases we have to be, make sure that well, is there an element of doubt but clearly that's where the unlikely category comes in and these are patients who are being said, well it's probably related to their targeted agent and you know, clearly that's probably likely not the case. But what that does is it really contaminates the whole database in terms of what is the causality of these toxicities. It's a huge problem worldwide and we certainly see that when we're having to look at data from large international studies where you have groups who probably don't have a lot of experience with either the chemo or the targeted agent. And making these attributions it really kind of make a mess of the database.- S05

- Mostly I find you know I tend, I agree with, with the conclusions they come to and sometimes um, I think there's a tendency to over report disease-related symptoms as being related to the investigational agent by the invest, you know, to be reported by the investigator. - S08
- And so in that setting there's a discrepancy between what the investigator feels and what the medical monitor feels. - S08
- Well I think that there are, I mean I think you know, if you start sort of labeling a drug as having you know x, y and z side effects and in fact they're in fact they're side effects related to the disease then you know, um that's a problem. But on the other hand does it, how does it limit development of the, the agents. I'm not certain, well I'm not less certain that it's going to limit development of the agent. - S08
- Well, I think you can overcall things that, and say that they're related when they're not. [mmm hmm] Um, and then that leads to for the drug companies to sort out or, or you know, whoever the sponsor is in determining are these or are they not? And I think um, it would be beneficial at some point to follow through on the other end of things to see what it means when you're on that end. [what do you mean on the other end?] Like a CRO getting this information in and saying now, you know, oh well what does that mean, the word, how you take it and what did they do with it from that point. Because I mean we submit the information but what happens on that side, but I think.- S09
- I think the biggest implication would be that if a drug gets attributed to have a set of adverse events that are quite serious then that may preclude further study of that drug, that might stop the trial. And if you're looking at a dose escalation study where you're escalating to your next dose based on the tolerated dose, you're now saying that there's some side effects. Well you might not go to the next dose level, or you're recruiting more patients to that particular cohort level so subjecting more people to the drug than may be necessary in a clinical trial. So the issue of not, of a potentially very good drug not being taken further because of the concerns of the adverse events, that's going one way. And the other way if you don't attribute the causality, a potentially dangerous drug could come to market without the proper, or with concerns about adverse events.- S10
- Um, an implication could be the fact that drugs aren't being marketed or aren't moving on to different phases of trial because causality has been improperly assigned. It could also on the very opposite side of the spectrum, it could also lead to harmed patients, it could lead to death in patients. A whole array of things, I mean it could obviously affect the statistical analysis of the study, it can affect everything.- S11
- So you could in one situation attribute something to an entire one set of the, the most serious and if it's this and you don't acknowledge it, that's dangerous for future patients in the study. [right] If it's, if it's you know, this and you label it as this, you could be potentially closing a trial that presumably was well thought out and had a good hypothesis and the hypothesis could end up being rejected. [implications] Potentially [yeah] I

mean if you polarize the extremities yeah, most of the stuff is not going to end up being that extreme, it's going to be in the middle but.- S12

- Well there's definitely implications in serious adverse events, and, and association, obviously if you put it wrong then there's misinformation. If it is associated and you don't think it is then that, that's probably the more harm there because we need to be aware, particularly in Phase Is that we need to be aware of and people think oh it's very unlikely I'm going to put it not related but then obviously that's information that the physicians and the patients in particular need to know about. So I think the worst is an association that is there but one grades as not associated and, and harm could be done to patients. The other extreme is people, and I see this a, a lot because you have to, as the PI on the trials you have to signoff on all the REB submissions to the REB. People that put everything is associated creates lots of paperwork. Where its very clear in reading through their SAE this was not drug related, this was disease related. And to me that doesn't do any harm to patients which is good but it creates extra paperwork for the CRAs, for the nurse, for us, for the REBs and to me that's more irritating when it comes from all around the world, you know you get. [yeah] People could be, could think a little I think, I don't know, think a little bit more clearer in terms of what they think is associated and perhaps those that are not associated would save the.- S13
- Well you can clearly overlook, worst possible thing would be that you actually don't report a side effect which is actually a side effect, from, from the drug. That may really happen, but I think one of the existing problems is that the frequency of those side effects maybe under reported.- S14
- Overlooking it altogether is certainly worse [yeah] but I think [it's also important] a serious adverse event, if a serious adverse event is seen in relationship to this more often then at some point we, we report it. But I think the frequency may then be under reported. But the key, overlooking a side effect or not reporting a serious adverse event which is actually part of the side effect profile, that's probably the worst, the worst thing.- S14
- The opposite is true too, if you , if you report an SAE which is not related to the drug [mmm hmm] then that can cause a considerable, can have considerable sincere consequences for the, for the drug and the development of the drug.- S14
- Worse case scenario that you delay or you stop the development of the drug. I mean imagine that a patient dies on a Phase I study and you assign the death as possibly related to the study drug and it wasn't. Something like this can kill, kill a drug in the development or at least considerably delay it or cause a lot more costs for the, for the company or whoever develops the drug to do additional testing and stuff like this.- S14
- Um, well, of assigning them poorly? It's either you under, or whatever event it was so you're compromising safety of future patients who might go on this treatment if you um, rule that it wasn't related to the drug. Or you might over, you know if you say that everything is related to the um, to the

investigational drug then you're over, over rating it as to whether the drug is causing problems. So it's pretty serious.- S15

- Well the potential ramifications of that is the drug might not go out to market and it might be a potentially legitimate drug. [okay] Because describe SAEs or have SAEs that might not really, that are manageable or might not really be 100% related to the drug. Especially if you pick a poor group of people who you know always get admitted for nausea and vomiting because they have a poor ECOG status. And it could be that they were just very poor patients initially to put on treatment.- S15
- I think there's two big concerns. One is if you assign causality and say it's related improperly then it might tarnish a good drug and stop dose escalation in a way that wouldn't be appropriate. Alternatively if you ignore it, it might cause further toxicities in others and be potentially dangerous to other patients. I think it's a very dangerous thing. I also think that sometimes as oncologists we tend to minimize rather than maximize because we're used to toxicity with drugs and that can be dangerous.- S16
- I think most of the doctors who do a lot of clinical research are aware of the fact that you don't want to underestimate the toxicity of a drug. But at the same time you don't want to assign every single adverse event to the drug some will not be due to the drug. So you usually end up in the, this is a possible to probable consequence of the drug if it's in the grey area where there could be many reasons why the patient had an adverse event.- S17
- One always worries if an investigator who is on, perhaps working with a drug company may wish to minimize adverse events because they really want this drug to be a success or acceptable. And it need not necessarily be driven by egregious opportunities around receipt of research funds, it may be because they get sort of um, too invested in the drug itself and wanting it to succeed or wanting their career to succeed or something of that nature. But that can induce investigator bias. Um, on the other hand you can have some investigators who um, will always attribute causality to the drug because they rather simplistically think if anything bad happens it must be the drug.- S17
- Um, I think any time with an investigational agent, like I said your antenna are fairly high up and you probably are more likely to ah, to lean on the side of, you don't want to harm a patient or subject to harm to assign causality where it may not have. Like assign a higher level of attribution even if it may not have been. So you know, when in doubt the diagnosis of exclusion is going to be that it's, it's the investigational agent. [yeah] So, and that may be unfair to the agent under development right. [mmm hmm] So it's just your level of, you scrutinize it more, like I said a more conservative approach to when in doubt, better to say it's possibly related than not. Those are, and no tool.- S18
- I probably don't give it as much thought as, as I should. I mean, I guess the real risk is that if people are falsely ascribing SAEs to the drug when

it's really the cancer then you could potentially throw out a good drug.- S21

- And I guess the converse is true too that if you don't, if you don't adequately report the toxicities then you might be introducing a drug to the market that is dangerous.- S21
- But it may not be quite that easy to do with chemotherapy, even in the, even off trial, but it's particularly difficult to do that on a trial because you know that you might sabotage you know, the intent of the study by just unnecessarily stopping. You know, I think the onus on an investigator and somebody who's responsible for treating the patient on a trial is quite high really because they have the ability to undermine the trial by making a fallacious attribution. You know because something might have happened you know, they got gastro because they ate something at some restaurant or something and then you say well it's the drug and you take them off the drug. Well then you undermine the whole enterprise you know which isn't just that trial, it stretches back over probably 15 years of work and money and investment. And it's so easy to undermine it by making, by casually making the wrong attribution.- S22
- So there's two kinds of mistakes you can make. You can make a false positive attribution or you can make a false negative lack of attribution, when in fact you should have.- S22
- The real, the really difficult issue is where you would have a situation where you would have to stop the study drug or reduce the dose of the study drug. There I think it becomes particularly difficult and particularly important that the correct decision is made. If you're simply going to say well you can treat this with a bit of Imodium or some heparin or something it doesn't really matter. But where you're forced to interfere with the conduct of the study and the administration of the new drug that's where it becomes acutely important to do the right thing.- S22
- Because I think you can falsely label a drug with all sorts of um, toxicities that have nothing to do with it.- S30
- Um, and it can go both ways, if you only see a very small number of patients you may underestimate or under-relate particular symptoms to, to the drug. And the same thing can also happen where if, if you just decide that every bad thing that happens to a patient is going to be possibly attributable then, then not only do you jeopardize the development of a drug but you also, those things all get added to patient consent forms and they muddy the waters for patients.- S30
- So you're assigning causation when maybe it's not it may be something else. So as a company I think they're obligated to list that as a part of their um, their package. Maybe not, maybe they don't take into account certain timeframes. Maybe they have a tool.- S31

Theme 5: Competing Goals

Definition: Within the process of assigning causality these professionals' primary interest is to be as accurate as possible and while considering the safety of their patient. However their goals compete against other goals of the trial whether it be the workload, time, or the development of an agent.

Subthemes:

- Patient safety vs. drug development
- Accuracy vs. extreme workload and drastic timelines
- Financial pressures
- Patient vs. physician

Quotations:

- Well if you have, ah, ah following the patients with this and it takes how many minutes or hours to do it, it's very costly [it adds up] it's very labour intensive.- S03
- And the ICH/GCP guidelines which this is part of is, is, ah, is making it very, very difficult to do this sort of research and it's unfortunate because you know, we need to study new drugs, we need to, yeah.- S03
- Yeah, you know, my concern is sometimes not enough attention is paid or they don't understand sometimes what the implications are so they don't give it enough time, they don't understand it.- S03
- From a causality point of view, I mean there's more stress if the adverse event is of a more serious magnitude in terms of determining how related it is to the trial medication.- S04
- There's an awful lot of pressure when you're doing early phase studies with a small biotech company. They, there's a lot riding on, on, you know, there are the issues of well are you going to torpedo their only drug or just from a financial point of view, with toxicities that are going to expand the dose level. That's gets in and take longer for the study to complete, those have big financial implications. On the other hand our, our first responsibility is to the patient and if not I think making sure, a lot of pressure from the smaller companies. And I think the other pressure is just the sheer volume of the adverse events you know, here are the ones from the last couple of weeks. So it's just huge volumes and they all, and everybody wants them done within kind of 24/48 hours and it just becomes impossible to do. On some level there needs to be, and a lot of these are these ones that you know it's clearly the chemo drug and probably really isn't related to the study drug. But there's, probably half of those are those

kind of things that have been generated, probably inappropriately because of the experience of the people who, it's a problem. It's a huge workload and unless we're handling them consistently I'm not sure we're going to be any further ahead.- S05

- Um, well there, you know, there, I think one has to fight, now this is a more of a perception, I don't have any examples. But there's a risk that the sponsor may want, may prefer you to go to an unlikely conclusion. That I disagree with.- S06
- No I haven't because I've stubbornly just said well that's my final answer, so I've never felt any, any sense of coercion. Obviously, you know, inherently results in more work for somebody but ah, in the Phase 1 setting I, I, I think ultimately it's the sponsor's in their best interest to fully understand what their drug is doing and what it's potential effects are. But one does have to be fairly stubborn in that regard.- S06
- The challenge is that the good Epi group who can run trials in an academic setting are going to be approached by drug companies. And you need a lot of money, those staff have to be paid and there are costs to the clin epi group and that's a lot better than a local academic.- S07
investigator say getting a grant for 100,000 bucks and he can give you a \$1000 bucks. I think they're, they're, the risk I think comes in the academic setting when the institute needs to kind of step up I mean today that's being done, certainly here's its done so it's, but I don't know about other centres across the country.- S06
- Not too much, but then again I'm not the one that the sponsors contacting when they call you and go are you sure that this is what you think it is? and stuff like that. I've had one of those calls where they'll call back and they'll say is this the way you want it? And you just go back to the physician and tell them they want to reconsider. And sometimes the physician is, will stick to their guns and sometimes they will re-think it or whatever.- S07
- Well I think it's based on what's been listed in the protocol and possibly the investigator brochure. But really do you have time to look at an investigator brochure every time? No.- S08
- And then you have, because different companies will approach it differently and so then you have AstraZeneca with their reports. The company sort of reports basically they, they want to downplay um, these and so their stock standard line is that you know, such and such a side effect is not listed in the investigator brochure, the implication being well it can't be related. So you know they take the, so you've got to look at it with, it's somewhat helpful but somewhat tedious. - S08
- No, cause what happens, they'll send us the report and then it's up to us to how we deal with it. I mean they have to be forwarded to the REB and the internal documentation that we do is more about sort of thinking for ourselves whether we want to make consent changes. Whether we see something which is happening you know, with um, severity or a frequency that would justify making a change to the consent form. And that doesn't

happen very often, in part because you know, we tend to wait for, because periodically there will be an update to the investigator brochures and then they'll consider if the consents need to be updated. - S08

- Sometimes in some places for some companies you know the serious adverse event would be mucositis, diarrhea and dehydration. And other places and I guess the NCIC in particular, I mean our recent experience, is that they say well the drug doesn't cause dehydration, the diarrhea and the mucositis does. So you have primary adverse event and then you have secondary effects from that [right]. And then really only want the primary event reported as the serious adverse event and then what's secondary to that is covered in the description of the serious adverse event. - S08

- S08: [that's a bit of a challenge] It is and some of that is sort of developing a better understanding of what individual sponsors want or expect. But on the other hand maybe there should be you know, greater consistency. - S08

M: You find that there is variation among the sponsors as to what it is that they want and expect.

S08: Yeah.

- Um, well they come back and say well are you sure that's related? [mmm hmm] right [yeah] you know. No I'm not sure but I'm not willing to say it's not, you know.- S09

- M: Sort of the pressure to keep the drug development process moving I guess.

S09: Um, hmm, um, hmm. Yeah, very much so. And, and I think some of the pressures come around too is you know to put patients on study and sometimes that feels more, that's more the goal rather than the safety of the patient. I think we rely on the companies to monitor these studies and when they don't, especially the early phase studies, and when they don't there's a huge problem with that. I'm not perfect, and they're not either but I think they then have the responsibility to monitor those studies and get those forms back into data management so they can make the proper queries that will probably, that could correct anything that you're not even aware of.- S09

- Well if you're involved in industry studies then certainly there's some pressure from, not so much for assigning causality but continuing. So if you've had someone who has had an adverse event and you want to dose reduce them or hold off treatment for a little while sometimes there is that pressure to continue with the study. So in that sense you could think well maybe if you had assigned them a possible as opposed to a probable relationship then you could, you could be pushed to continue with the study. But you always have to keep the patient's safety in mind [right] at the end of the day so, so that's what you go by.- S10
- But I must admit I really haven't had that much pressure in terms of treating the patient. It always comes down to the patient's safety and that's what you go by.- S10

- Again, I'm not really sure that's optimal especially considering how, you know, little time everybody has these days.- S11
- Um, I mean to start out with the very basics, a lot of, a huge workload involved, um, in doing it poorly and that, I mean it could be anything. Just from the workload involved in SAE's, even the reporting, all the different avenues it needs to go through.- S11
- Who's kidding who, they're busy and overworked, um, and trials are a lot of paper work. So I think that's possible, I certainly don't think there would be malicious intent [no] but I, but I do think that you know, even time constraints that sort of thing could have, play a factor in that.- S11
- So if, if, there's an SAE that, that comes out of that, that has So if, if, there's an SAE that, that comes out of that, that has implications for notifying sponsors, the sponsor notifying the regulatory agencies and the company, there's timelines for doing so. The nature of enough AEs may influence the conduct of the study [how does it influence?] so misrepresent, well a series of SAEs may [9:51].- S12
- It's just very practical and if ah, I mean there is a bureaucratic process that is time consuming that if you assign an SAE versus not that somebody's going to have to do a lot of work and meet timelines and set a whole ball rolling.- S12
- I think you then have the issue of the sponsor, and sponsors, sponsor may influence. [okay, how so?] I think in general from what I've seen, sponsors will tend to, tend to things that are expected, the, if the consequence is an expected one and it's tended less to be labeled serious adverse event even if it's expected but the degree and the severity wasn't, that's a tricky one, you give an agent.- S12
- I mean I think um, basically um, if we all had more time in our day it would probably be easier to do it. The SAE has to be filled in within 24 hours. I mean that's another issue, why 24 hours? what's the urgency? By the time we receive it, we send it off to the sponsor, it goes to REB, there's going to be a lag time anyways. And you don't expect things to, you know, maybe grade 5 toxicities where you have a death, maybe that should be 24 hours. But I, I don't know why an SAE can't be 48, so you don't feel that pressure to have to. Not that, I think we do it just because we feel a pressure, but again I think we just said 24 hours and that's just been the rule that's been adopted all along right. [right] I actually don't see the rationale of 24 versus 48.- S13
- Well I think the only external pressures is obviously be accurate as possible. And so you know we're part of the, part of the Princess Margaret Consortium and you know a couple of the NCI trials, you know the NCI physician from the US is emailing me in terms of causality, so obviously there are pressures to be as accurate as possible. But sometimes you really don't know if it's associated or not.- S13
- Um, probably the sponsor wanting an answer right away of what the cause, because sometimes you don't know, it's hard to make a decision on one patient, like the first patient that presents. Especially if that

particular patient has multiple problems and it's possible that it could be their disease or a component of their disease that's causing the symptom or the, the abnormal lab result.- S15

- The first issue is how quickly can you really assign it? Often you know, you need to report within 24 hours. Within 24 hours you may report, the person came in with chest pain, da, da, da, and you don't have any real idea if it's related or not.- S16
- I think sometimes, sometimes you're in such a rush to get the CRF done that I think you don't necessarily spend enough time. And I think one of the other problems is we get so many reports about drugs, you know like alerts [safety letters?] safety letters that sometimes everybody doesn't know these things and may not know if it's related or not. I think keeping up with the safety letters is hard, [just because you get so many of them?] mmm hmm and not really knowing the drug well.- S16
- The timeline, it's mainly the timeline and the pharmaceutical company.- S16
- And if you're so busy or have not done your homework in terms of reading about the drug, or don't have the time to go look it up. So you know, basically just having a busy clinic and being busy at work can lead you to mis-attribute these things right.- S19
- Third parties, um, our CRA's sometimes want things attributed in a certain way.- S19
- Yeah, I was just thinking they're, when you look at attribution of adverse events, I mean they're basically the people you're working with [yeah and they want] you think you're filling out a CRF and then um [they] they want an attribution level. And ah, sometimes they have their opinions about what the attribution is and they're different from [yours] mine. You know, not a lot but um, that just in terms of explaining to them and then they have to change their forms [yeah, yeah] and if they've already submitted the forms a certain way. Ah, in affect you're creating more work for them, ah, so that does, I don't like to create more work for the people I work with. So I do feel a little but of pressure there, but ah.- S19
- I guess, I guess one of the biggest challenges these days is that if we, people have enough time to rigorously evaluate all the possibilities in a very busy clinic setting. [yeah so] The time to sit down and really fully go over everything with the patient in terms of what's new by history and do a good physical examination.- S20
- Um, I think everybody's under severe time pressures these days and it makes it, it's um, you need to have a dedicated infrastructure to do good Phase I and II studies.- S20
- Yeah, that's a very valid question, sometimes I will have a patient who is having a serious toxicity and I want to stop the drug and the patient is pressuring me to keep on the drug. And you know, if you are going to keep them on the drug then maybe you have to under report the toxicity.- S21

- No, I don't, I don't think so, no, it's mainly the example I can think of is patient's pressuring me to keep them on a drug when I'm not sure that's to their, you know in their best interest.- S21
- I guess, I keep coming back to this, but keeping it simple and brief because there are a lot of competitors for a trialist's attention, you know, like there are a lot of time constraints and something more simple that would be best.- S21
- On the other hand you don't want to be paralyzed by uncertainty because if you're in a busy clinic you can only tolerate paralysis for so long [right] you have to make some kind of a decision.- S22
- Well I think you know, they have to make a judgment in a hurry, so there's a concern straight away, they're on the busy machine in the clinic and they have to, you know, somebody puts some form in front of them and they kind of, you know, they've got two pens, one pen in their left hand and one pen in their right hand and they're hitting the typewriter with their nose and looking at the screen and trying to do four things at once and the telephone is ringing and so on. It really is a zoo as you know, so they have to make hurried decisions, so that's my one, that's my number one concern.- S22
- I have seen situations where some pressure, let's say that the pharmaceutical company maybe had a different viewpoint about what was said, you know without being specific I've certainly seen that. I think most people have, most people that deal with pharmaceutical companies realize that they're obviously coming from a certain angle. And that they may have a different interpretation, sometimes, I think sometimes they're right. I think, I'm not saying they're always wrong but certainly they have a viewpoint [sure] which they express you know.- S22
- I think you know, if a patient is sick in a way that taxes the resources of the cancer center and the hospital, I think you know, there's certainly pressure not to carry this on beyond what's reasonable. And you know, that's, that's understandable and inevitable.- S22
- Time, the physician's time.- S23
- Well it's the companies they want to get their drugs to market and sometimes you get a little pressure from them you know? [to do what?] Well to just to confirm yes this is related particularly if it's nasty, nasty stuff. There's a couple of companies out there that don't think twice about picking up the phone, you know, asking you to review with the physician, that's fine we'll review it but ultimately we're not here for the trial. Well we're here for the trials, but we're here for the patients and so we're not going to cause them any harm if we can help it.- S23
- Lack of time probably. [just time pressures, yeah, okay that would seem reasonable].- S24
- Yes I guess, um, I was going to say something similar to that, that they might be making decisions quickly without really going to source, some sort of source or really knowing.- S25

- Um, well I find the companies, well they don't always agree and then ah, [with your assessment?] with our assessments. And you see that often in safety reports that come through, it's tends to be always a possible or probable assessment when it really may not be necessary. But not a major pressure other than they want to know what the causality is you know, with that initial, if it's an SAE for example [yeah] they want to know that right away because they have to send that out to other sites. [yeah] So you know, that's the pressure there to sort of um, get that answer quickly. And because we don't want to make that ultimate decision they may be getting our assessment initially that might not be the correct one so I guess that would be a concern or a pressure for me [yeah] to get the physicians ultimate decision on [right]. Because they want the information quickly right with an SAE so.- S25
- Ah, yeah, they could do that for sure, they might phone us, or during monitor visit they might um, sort of query it and ask questions about why we, thought it was related or not. And then give us their reasons why they think it should be different and want us to change it and we might not always want to. So there's, there's always that happens, usually they would speak with the physician, we'd have them speak directly with them so they would discuss their reasons for their assessment. But it does happen.- S25
- Ah, none [can you recall a time?] none really, I mean there's, the only pressure that you feel um, is the sort of sense of urgency of, because you know you have to fill out the SAE report within 24 hours and all this sort of stuff. You may not have all the information and you may make an original, you may make an assessment that subsequently you change or becomes clearer as time goes on that something else is in fact happening and you want to change your mind about something. Which is, which is fine and you do, do that but I think that sometimes, I don't know that you should necessarily have to assign the causality right away. I mean I think reporting the SAE right away and saying this is what's happening and we're monitoring the patient and these are the steps we've taken. And we'll, you know, as things evolve we'll let you know what we think actually happened, rather than saying yes we think this is study drug related within the first 18 hours when you don't, you may not necessarily have all the facts yet.- S26
- Like I think that whole 24-hour, like I understand that we need to report the event but I think the causality part of it should be delayed until after you have the facts. And then you can say okay really I think this is you know.- S26
- So anytime they asked for anything to be changed I would leave those queries up to him and 9 times out of 10 he would not change them. [oh that's good] Because, but then it gets annoying and then you start to second guess and wonder why are they even asking if the investigator is ultimately responsible for the data and not some data entry person a

million miles away who has no idea what is really going on. Why are they second guessing this, what are they really after?- S28

- Well with smaller drug companies you tend to get more queries about why did you assign this as attributed or not attributed? You know, what do you think the underlying pathophysiology is? and so you know, smaller drug companies particularly when their entire livelihood depends on, on a single agent will, will be, will, I don't know if pressure is the right word but they will definitely discuss extensively how and why you've chosen that something is related.- S30